IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	**REDACTED**
	)	**PUBLIC VERSION**
	)	Civil Action No. 05-356-SLR
	)	(consolidated)
	)	

PLAINTIFFS' POST-TRIAL ANSWERING BRIEF

APPENDIX II:
TRIAL EXHIBITS

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Date: August 22, 2007

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TRIAL TRANSCRIPT EXCERPTS

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TRIAL EXHIBITS

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APPENDIX III:
TRIAL EXHIBITS AND ADDITIONAL AUTHORITIES

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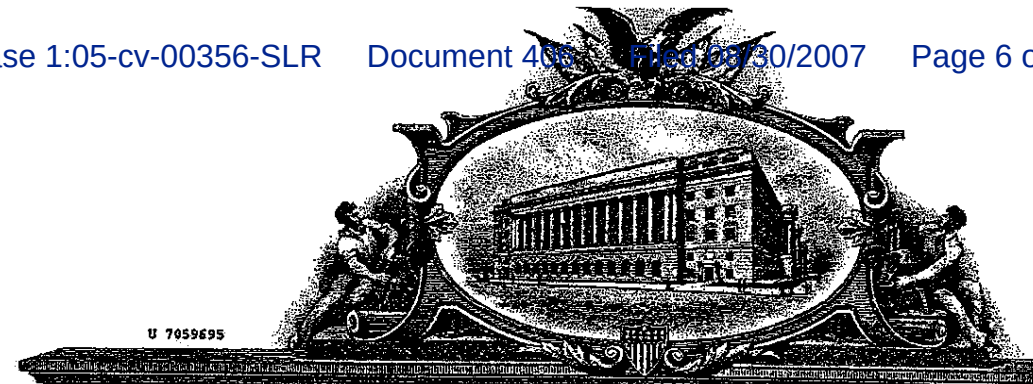
69		United States Patent and Trademark Office Memorandum, "Supreme Court decision on *KSR Int'l Co., v. Teleflex, Inc.*", May 3, 2007

EXHIBIT 1



U 7059695

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 27, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *4,663,318*
ISSUE DATE: *May 05, 1987*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Plaintiff's Exhibit
PX - 1

United States Patent [19]
Davis

[11] **Patent Number: 4,663,318**
[45] **Date of Patent: May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] Inventor: **Bonnie Davis, 17 Seacrest Dr., Huntington, N.Y. 11743**

[21] Appl. No.: **819,141**

[22] Filed: **Jan. 15, 1986**

[51] Int. Cl.⁴ **A61K 31/55**
[52] U.S. Cl. **514/215**
[58] Field of Search 514/215

[56] **References Cited**

PUBLICATIONS

Chem. Abst. (81)–72615z (1974).
Chem. Abst. (86)–115157z (1977).
Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86, pp. 1125–1130.
Kendall et al., J. Chem. & Hospital Pharmacol., (1985) 10–327–330.
S. Chaplygina et al., J. of Highest Nervous Activity vol. XXIV 1976 Issue 5, pp. 1–4.
Krause, J. of Highest Nervous Activity, vol. XXII, 1974, Issue 4.

Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

7 Claims, No Drawings

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METHOD OF TREATING ALZHEIMER'S DISEASE

GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163–8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anesth. Scand. 24:166–168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1–50 mg/ml more commonly 5–40 mg/ml, for example, 5–30 mg/ml or 10–40 mg/ml, typically 20–30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5–1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5–5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50–300 mg per day to a patient of a body weight of 40–100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100–600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945–952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to

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administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5–1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50–300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10–2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100–600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

* * * * *

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EXHIBIT 2

THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

March 26, 2007

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *06/819,141*
FILING DATE: *January 15, 1986*
PATENT NUMBER: *4663318*
ISSUE DATE: *May 05, 1987*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Plaintiff's Exhibit
PX - 2

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Rev. 8/78) 4663318

SERIAL NUMBER (Series 1979)	PATENT DATE	PATENT NUMBER
819141	MAY 5 1987	

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
06/819,141	01/15/86	514		125	

BONNIE DAVIS, HUNTINGTON, NY.

CONTINUING DATA********************
VERIFIED

FOREIGN/PCT APPLICATIONS**********
VERIFIED

FOREIGN FILING LICENSE GRANTED 02/21/86 ***** SMALL ENTITY *****

Foreign priority claimed / 35 USC 119 conditions met	☐ yes ☐ no / ☐ yes ☐ no	AS FILED	STATE OR COUNTRY	SHEETS DRWGS	TOTAL CLAIMS	INDEP CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO
Verified and Acknowledged / Examiner's Initials			NY		7	1	$ 170.00	U 5631

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NEW YORK, NY 10023

OK

TITLE
METHOD OF TREATING ALZHEIMER'S DISEASE

U.S. DEPT of COMM.-Pat. & TM Office — PTO-436L (rev

PARTS OF APPLICATION FILED SEPARATELY	PREPARED FOR ISSUE
	(Assistant Examiner) / C. Sullivan (Docket Clerk)

AT ALLOWANCE					EXAMINED AND PASSED FOR ISSUE
SHEETS DWGS.	FIGURES DRWGS.	CLAIMS	CLASS	SUBCLASS	Stanley J. Friedman, Primary Examiner (Primary Examiner) 125 (Art Unit)
—	—	7	514	215	

RETENTION LABEL		Estimate of printed pages: Drawing(s) / Spec(s)	Issue fee due (est.)
	1-27		$380.00
		Notice of allowance and issue fee due (est.) — Date mailed: 12/30/86	Date paid: 1-20 87

06/819,141

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PATENT NUMBER and ISSUE DATE
4663318

U.S. UTILITY Patent Application

Duplicate File Original File Lost

06 819,141

APPLICATION NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
06/819,141	1/15/86	514		1305	

(FACE)

NOTICE OF ALLOWANCE MAILED	Assistant Examiner	CLAIMS ALLOWED	
		Total Claims	Print Claim for O.G
ISSUE FEE		DRAWING	
Amount Due / Date Paid		Sheets Drwg. / Figs.Drwg. / Print Fig.	
	Primary Examiner		
☐ TERMINAL DISCLAIMER	PREPARED FOR ISSUE	Application Examiner	

WARNING: The information disclosed herein may be restricted. Unauthorized disclosure may be prohibited by the United States Code Title 35, Sections 122, 181 and 368. Possession outside the U.S. Patent & Trademark Office is restricted to authorized employees and contractors only.

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SEARCH

Class	Sub.	Date	Exmr.

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.

0191

Computer search

3/21/86

SEARCHED

Class	Sub	Date	Exr
514	215	3/26/86	
		9/26/86	

INTERFERENCE SEARCHED

Class	Sub	Date	Exr
1	215	9/24/86	

PRINT CLAIM(S): 1

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SYMBOLS	STATUS
✓	Rejected
=	Allowed
– (Through numeral)	Canceled
+	Restriction requirement
N	Nonelected invention or species
I	Interference
A	Appeal
O	Objected

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ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION			
ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
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INDEX OF CLAIMS

✓ ..... Rejected – (Through numeral) ... Canceled N ..... Non-elected A ..... Appeal
= ..... Allowed + ... Restricted I ..... Interference O ..... Objected

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If more than 150 claims or 9 actions staple additional sheet here

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019141

PATENT

Docket No. U 5631

Commissioner of Patents and Trademarks
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of

Inventor(s):

Bonnie DAVIS

NOTE: Patent must be applied for in the name(s) of all of the actual inventor(s). 37 CFR 1.41 and 1.53(b).

WARNING: If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.

For (title): METHOD OF TREATING ALZHEIMER'S DISEASE

Enclosed are:

1. **Benefit of Prior U.S. Application (35 USC 120)**

NOTE: If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, e.g., where (1) the parent case is not to be abandoned (e.g., a divisional continuation-in-part) or (2) where the parent case is an International Application which designated the U.S., then check the following item and complete and attach ADDED PAGES FOR NEW APPLICATION TRANSMITTAL.

☐ The new application being transmitted claims the benefit of a prior U.S. application and enclosed is added pages for new application transmittal where benefit of a prior U.S. application claimed.

2. **Papers Required For Filing Date Under 37 CFR 1.53(b):**

4 Pages of specification
1 Pages of Abstract
1 Pages of claims
___ Sheets of drawing
☐ formal
☐ informal

In addition to the above papers there is also attached:

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this New Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date January 15, 1986 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number EB345444I addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

GERALDINE MELENDEZ
(Type or print name of person mailing paper)

(Signature of person mailing paper)

NOTE: Each paper or fee referred to as enclosed herein has the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 CFR 1.10(b).

3. Declaration or oath

[X] Enclosed

[X] original

executed by *(check all applicable boxes)*

[ ] inventor(s).

[ ] legal representative of inventor(s). 37 CFR 1.42 or 1.43.

[ ] joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.

[ ] this is the petition required by 37 CFR 1.47 and the statement required by 37 CFR 1.47 is also attached. *See item 10 below for fee.*

[ ] Not Enclosed.

WARNING: Where the filing is a completion in the U.S. of an international application under 35 U.S.C. 371(c)(4) the declaration can be filed after 20 months from the priority date, in which event it must be filed within 22 months from the priority date with payment of a surcharge and failure to comply with this requirement will result in abandonment of the application. The provisions of § 1.136 do not apply to the 22 month period. 37 CFR 1.61(b).

NOTE: Where a declaration is not available or where the completion of the U.S. application contains subject matter in addition to the International Application treat the application being transmitted as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL.

[ ] Application is made by a person authorized under 37 CFR 1.41(c) on behalf of *all* the above named inventor(s). The declaration or oath, along with the surcharge required by 37 CFR 1.16(e) can be filed subsequently.

NOTE: It is important that all the correct inventor(s) are named for filing under 37 CFR 1.41(c) and 1.53(b).

[ ] Showing that the filing is authorized. (*Not required unless called into question. 37 CFR 1.41(d).*

4. Inventorship Statement

The inventorship for all the claims in this application are:

[X] the same

or

[ ] are not the same and an explanation, including the ownership of the various claims at the time the last claimed invention was made, is submitted.

5. Language

[X] English

[ ] non-English

NOTE: An application including a signed oath or declaration may be filed in a language other than English. A verified English translation of the non-English language application and the processing fee of $26.00 required by 37 CFR 1.17(k) is required to be filed with the application or within such time as may be set by the Office. 37 CFR 1.52(d).

NOTE: A non-English oath or declaration in the form provided or approved by the PTO need not be translated. 37 CFR 1.69(b).

WARNING: If the translation of the international application has not been submitted by the applicant within 20 months from the priority date, when the filing is a completion in the U.S. of an international application under 35 U.S.C. 371(c)(2), such requirements must be met within 22 months from the priority date. The payment of the processing fee set forth in § 1.445(a)(6) is required for acceptance of an English translation later than 20 months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 do not apply to the 22 month period. 37 CFR 1.61(b). The translation into English need not be verified. 37 CFR 1.61(a). The processing fee for filing the translation after 20 months from the priority date is $26.00.

☐ A verified English translation of the

check applicable item(s)

☐ specification and claims

☐ declaration

is attached.

5. Assignment

☐ An assignment of the invention to _____

_____

☐ is attached

☐ will follow

7. Certified Copy

Certified copy(ies) of application(s)

(country)	(appln. no.)	(filed)
(country)	(appln. no.)	(filed)
(country)	(appln. no.)	(filed)

from which priority is claimed

☐ is attached

☐ will follow

NOTE: Must be referred to in oath or declaration. 37 CFR 1.55(a) and 1.63.

8. Fee Calculation

CLAIMS AS FILED

	Number filed		Number Extra		Rate	Basic Fee $340.00
Total Claims	7	−20= 0		X	$ 12.00	0
Independent Claims	1	−3= 0		X	$ 34.00	0
Multiple dependent claim(s), if any					$110.00	0

☐ Amendment cancelling extra claims enclosed

☐ Amendment deleting multiple dependencies enclosed

☐ Fee for extra claims is not being paid at this time

NOTE: If the fee for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 CFR 1.16(d).

Filing Fee Calculation $ 340.00

9. Small Entity Statement

☒ verified statement that this is a filing by a small entity under 37 CFR 1.9 and 1.27 is attached.

Filing Fee Calculation (50% of above) $ 170.00

NOTE: Any excess of the full fee paid will be refunded if a verified statement and a refund request are filed within 2 months of the date of timely payment of a full fee. 37 CFR 1.28(a).

10. Fee Payment Being Made At This Time

WARNING: Where the filing is a completion in the U.S. of an international application under 35 U.S.C. 371(c)(1) the fee can be filed after 20 months from the priority date, in which event it must be filed within 22 months from the priority date with payment of a surcharge and failure to comply with this requirement will result in abandonment of the application. The provisions of § 1.136 do not apply to the 22 month period. 37 CFR 1.161(b).

☐ Not Enclosed

☐ No filing fee is to be paid at this time. (*This and the surcharge required by 37 CFR 1.16(e) can be paid subsequently.*)

☒ Enclosed

☒ basic filing fee	$ 170.00
☐ recording assignment ($7.00; 37 CFR 1.21(h)(1))	$
☐ petition fee for filing by other than all the inventors or person on behalf of the inventor where inventor refused to sign or cannot be reached. ($140.00; 37 CFR 1.47 and 1.17(h))	$
☐ for processing an application with a specification in a non-English language. ($26.00; 37 CFR 1.52(d) and 1.17(k) or 37 CFR 1.445(a)(6))	$
☐ processing and retention fee ($100.00; 37 CFR 1.53(d) and 1.21(l))	$

NOTE: 37 CFR 1.21(l) establishes a fee for processing and retaining any application which is abandoned for failing to complete the application pursuant to 37 CFR 1.53(d) and this, as well as the changes to 37 CFR 1.53 and 1.78, indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid or the processing and retention fee of § 1.21(l) must be paid within 1 year from notification under § 53(d).

Total fees enclosed $ 170.00

11. Method of Payment of Fees

☒ check in the amount of $ 170.00

☐ charge Account No. _____ in the amount of $ _____ A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 CFR 1.22(b)).

12. Authorization to Charge Additional Fees

NOTE: If no fees are to be paid on filing the following items should not be completed.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.

☒ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. 12-0425

☒ 37 CFR 1.16 (filing fees)

☒ 37 CFR 1.16 (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 CFR 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☐ 37 CFR 1.17 (application processing fees)

☐ 37 CFR 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 CFR 1.311(b).

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 CFR 1.311(b).

NOTE: 37 CFR 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application. . . .prior to paying, or at the time of paying. . . . issue fee". From the wording of 37 CFR 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

13. Instructions As To Overpayment

☒ credit Account No. 12-0425

☐ refund

Reg. No. JOHN RICHARDS

c/o LADAS & PARRY

Tel. No. ( ) 26 WEST 61st STREET

NEW YORK, N.Y. 10023

Reg. No. 31053 (212) 708-1915

SIGNATURE OF ATTORNEY

JOHN RICHARDS

Type or print name of attorney

P.O. Address

☐ Plus Added Page For New Application Transmittal Where Benefit Of A Prior U.S. Application Claimed

819141

PATENT APPLICATION SERIAL NO.

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

01/21/86 819141 1 201 170.00 OC

JAN 15 1980

170-10-201 A
819141

METHOD OF TREATING ALZHEIMER'S DISEASE

General Field of the Invention

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

Background Art

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta anesth. scand. 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615z.

The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-3, 1976.

CASE: U 5631

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

Summary of the Invention

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

Detailed Description of the Invention

Galanthamine can be administered in any convenient chemical or physcial form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Typical dosage

rates when administering galanthamine by injection are in the range 5-1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsule-making techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft gelatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal

model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacyin Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. Life Sciences 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5mg/5ml and 25mg/5ml concentration.

There have been reports that galanthamine can cause cardiac arrythmias. In such cases, it may be desirable to administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrythmias.

C L A I M S

1. A method of treating and diagnosing Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

CASE: U 5631

A B S T R A C T

Alzheimer's disease may be treated with galanthamine.

Case: U 5631

PATENT

Attorney's Docket No. U 5631

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION OR CIP APPLICATION)

As a below named inventor, I hereby declare that:

INVENTORSHIP IDENTIFICATION

WARNING: If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below next to my name, I believe I am the original, first and sole inventor (*if only one name is listed below*) or an original, first and joint inventor (*if plural names are listed below*) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD OF TREATING ALZHEIMER'S DISEASE

SPECIFICATION IDENTIFICATION

the specification of which: *(complete (a), (b) or (c))*

(a) ☒ is attached hereto.

(b) ☐ was filed on _____ as Application Serial No. _____ and was amended on _____ (*if applicable*).

NOTE: Amendments filed after the original papers are deposited with the PTO which contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims. See 37 CFR 1.67.

PCT FILED APPLICATION ENTERING NATIONAL STAGE

(c) ☐ was described and claimed in International Application No. _____ filed on _____ and as amended on _____ (*if any*).

ACKNOWLEDGEMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

☐ In compliance with this duty there is attached an information disclosure statement, 37 CFR 1.97.

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

(complete (d) or (e))

(d) ☒ no such applications have been filed.

(e) ☐ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION

Country Application No.	Date of filing (day, month, year)	Date of issue (day, month, year)	Priority Claimed
			☐ YES NO ☐
			☐ YES NO ☐
			☐ YES NO ☐

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION

DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (CIP)

(complete this part only if this is a divisional, continuation, or CIP application)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

(U.S. application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

(complete item below and add 35 USC 119 claim, if applicable)

☐ The attached 35 USC 119 claim for foreign priority for the U.S. application(s) listed above forms a part of this declaration.

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*List name and registration number*)

Leonard J. Robbins, 14894; S. Delvalle Goldsmith, 14383; Paul B. West, 18947; Lester Horwitz, 18998; Joseph H. Handelman, 26179; Peter D. Galloway, 27885; John Richards, 31463; Iain C. Baillie, 24090; John J. Chrystal, 26360; Thomas F. Peterson, 24790; Richard J. Streit, 25765; Richard P. Berg, 28145

SEND CORRESPONDENCE TO
Lester Horwitz
c/o LADAS & PARRY
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO: (*Name and telephone number*)
Lester Horwitz
(212) 708-1930

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURES

Full name of sole or first inventor Dr. Bonnie Davis

X Inventor's signature Bonnie Davis

X Date 12/26/85 Country of Citizenship USA

Residence 17 Seacrest Drive, Huntington, NY 11743

Post Office Address 17 Seacrest Drive, Huntington, NY 11743

Full name of second joint inventor, if any _____

Inventor's signature _____

Date _____ Country of Citizenship _____

Residence _____

Post Office Address _____

CHECK PROPER BOX(ES) FOR ANY OF THE FOLLOWING ADDED PAGE(S) FORMING A PART OF THIS DECLARATION

☐ Signature for third and subsequent joint inventors. Number of pages added _____

☐ Signature by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. Number of pages added _____

☐ Signature for inventor who refuses to sign or cannot be reached by person authorized under 37 CFR 1.47. Number of pages added _____

019141

Attorney's Docket No. U 5631

Applicant or Patentee: BONNIE DAVIS

Serial or Patent No.: _____

Filed or Issued: _____

For: METHOD OF TREATING ALZHEIMER'S DISEASE

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(b))—INDEPENDENT INVENTOR

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office with regard to the invention entitled _____

described in

- [X] the specification filed herewith.
- [ ] application serial no. _____, filed _____
- [ ] patent no. _____, issued _____

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

- [X] no such person, concern, or organization
- [ ] persons, concerns or organizations listed below*

*NOTE: *Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27).*

FULL NAME _____

ADDRESS _____

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____

ADDRESS _____

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

FULL NAME _____

ADDRESS _____

[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

BONNIE DAVIS
Name of Inventor

X Bonnie Davis
Signature of Inventor

X 12-26-85
Date

Name of Inventor

Signature of Inventor

Date

Name of Inventor

Signature of Inventor

Date

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 4461

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
06/819,141	01/15/1986 RULE	514	1205	U 5631

APPLICANTS

BONNIE DAVIS, HUNTINGTON, NY;

** CONTINUING DATA **********

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 02/21/1986

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDENT
35 USC 119 (a-d) conditions met	COUNTRY	DRAWING	CLAIMS	CLAIMS
Verified and Acknowledged	NY		7	1

☐ yes ☐ no
☐ yes ☐ no ☐ Met after Allowance
Examiner's Signature Initials

ADDRESS
C/O LADAS & PARRY
REG. NO. 31053 (212) 708-1715
JOHN RICHARDS
26 WEST 61ST STREET
NEW YORK , NY
10023

TITLE
METHOD OF TREATING ALZHEIMER'S DISEASE

FILING FEE	FEES: Authority has been given in Paper	
RECEIVED	No. _____ to charge/credit DEPOSIT ACCOUNT	☐ All Fees
0.00	No. _____ for following:	☐ 1.16 Fees (Filing)
		☐ 1.17 Fees (Processing Ext. of time)
		☐ 1.18 Fees (Issue)
		☐ Other _____
		☐ Credit

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
06/819,141	01/15/86	DAVIS B	U 5631

LESTER HORNTIZ
C/O LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

EXAMINER	
FRIEDMAN, S	
ART UNIT	PAPER NUMBER
125	2

DATE MAILED: 04/10/86

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-7 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-7 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).

10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. "Diagnosing" should be deleted from the claims. Such has nothing to do with treating. This point was telephonically discussed with Mr. John Richards on March 20, 1986.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-7 are rejected under 35 U.S.C. 103 as being unpatentable over Chem. Abstract references.

The art clearly teaches activities for the instant agent that would have value in treating effects of Alzheimer's disease.

Primary Examiner
Group Art Unit 125

Friedman:tgh
A/C 703
557-3920

4-4-86

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO. 819141	GROUP ART UNIT 125	ATTACHMENT TO PAPER NUMBER 2
NOTICE OF REFERENCES CITED	APPLICANT(S) Davis		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	Chem Abst. (81) – 72655 Z (1974).
S	Chem. Abst. (86) – 115157 Z (1977) –
T	
U	

EXAMINER	DATE
Friedman	3/6/86

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

MAIL ROOM SEP 11 1986 & TRADE MARK OFF

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bonnie Davis

Serial No.: 819,141 Group No.: 125

Filed: January 15, 1986 Examiner: Friedman

For: METHOD OF TREATING ALZHEIMER'S DISEASE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECEIVED
SEP 17 1986
GROUP 120

SIR:

AMENDMENT RESPONSIVE TO OFFICE ACTION OF APRIL 10, 1986

Please amend the application as follows:

IN THE SPECIFICATION

At page 1, line 12, change "anesth. scand." to read -- Anesth. Scand.--.

Page 2, line 29, change "from" to read --form--.

Page 2, line 33, correct spelling of --aids--.

IN THE CLAIMS

Claim 1, line 1, delete "and diagnosing".

R E M A R K S

The application is amended to meet the Examiner's rejection under 35 USC 112 by deletion of reference to diagnosis. This amendment is made without prejudice to the possibility of filing a divisional or continuation-in-part application directed to

---

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOSEPH H. HANDELMAN
(Type or print name of person mailing paper)

Date: SEPTEMBER 9, 1986

Joseph H. Handelman
(Signature of person mailing paper)

diagnosis in due course.

The amendments to the specification correct obvious typographical errors.

Alzheimer's disease is a major and growing problem in our society (see the paper by Hershenson & Moos in July 1986 Journal of Medical Chemistry submitted herewith). It is estimated that there are over 1,000,000 sufferers of this disease in the United States alone. Symptoms include depression, intellectual decline, memory loss, speech difficulties and muscular spasms. Little is known about the root cause of the condition and although useful results have been reported in some cases by treatment with physostigmine, its poor therapeutic index is likely to preclude its widespread use and there is no generally effective treatment available. As noted in an article by Kendall et al, submitted herewith, (J Clin Hos Pharmac (1985) 10 327-336), "The theoretical possibility of developing a long acting preparation of an agent with good brain penetration and possibly some selectivity of action towards the relevant cortical cholinergic system, must be seen as a major challenge for researchers working on Alzheimer's disease". Applicant currently has experiments underway using animal models which are expected to show that treatment with galanthamine does result in an improvement in the condition of those suffering from Alzheimer's disease. It is expected that data from this experimental work will be available in two to three months and will be submitted to the Examiner promptly thereafter. Furthermore, galanthamine is currently being used in Europe to assist in post-operative recovery from anaesthesia and so is unlikely to suffer the problems of possible toxicity encountered with physostigmine (Acta Anesth Scand (1980) 21:166).

The rejections under 35 USC 103 are respectfully

traversed. The rejection is based on two Chemical Abstract references noted in the specification. The first, by Kraus, is an abstract of a paper published in the Journal of Highest Nervous Activity Volume 24 (1974). The second is an article by Chaplygina and Ilyuchenok. Applicant has had translations of each of the original papers prepared and these are submitted herewith.

The Kraus article related to an investigation of the effects of various chemicals on short-term memory and the activity of the hippocampus in normal dogs. It concluded that the effect of galanthamine was about the same as that of strychnine and lower than that of phenamine and ethimizol.

The Chaplygina article describes work done on restoration of conditioned reflexes after memory in mice had been destroyed, for example, by electro-shock.

The Examiner's comment on this art, namely that it "teaches activities for the instant agent that would have value in treating the effects of Alzheimer's disease" is not entirely clear. However, apparently what the Examiner means is that since these articles indicate that galanthamine has an effect on improving short-term memory and on restoring memory after it has been destroyed, it would be useful in treating Alzheimer's disease. This is a non sequitur.

The mechanism of memory and indeed many brain functions are still only hazily understood at best. One cannot predict with any degree of confidence what the effect of any given chemical on a particular brain function or brain condition may be. While it is true that studies have shown that impairment of memory may result from certain specific factors varying from brain damage, though diminution of blood flow as a result of arteriosclerosis in brain arteries to chemical effects such as

thiamine deficiency in causing Wernicke-Korsakoff syndrome, the cause of "normal" establishment of memory and forgetfulness is still not understood. It is true that in Alzheimer's disease, there is memory loss. However, this is apparently associated with physiological changes in the brain including degeneration of nerve cells in the frontal and temporal lobes, damage in the neural pathways to the hippocampus and the creation of neurofibrillary tangles in nerve cells. There is no way of predicting that because a chemical may have an effect on memory in a normal brain (which is what is indicated in the cited references) it would have any effect on a brain that has suffered such physiological changes. To say that simply because a particular drug has some effect on a symptom caused by one underlying condition, it will have a useful effect on another underlying condition is clearly wrong. To predict that galanthamine would be useful in treating Alzheimer's disease just because it has been reported to have an effect on memory in circumstances having no relevance to Alzheimer's disease would be as baseless as predicting that one should treat impaired eyesight due to diabetes with drugs effective in ameliorating impaired vision due to other causes such as glaucoma. In fact, since the animals used in the studies of Kraus and Chaplygina were normal, an even more pertinent analogy can be made. The prediction that galanthamine would be useful to treat Alzheimer's disease because it is known to have an effect on memory in normal animals is as baseless as a prediction that impaired eyesight due to diabetes would respond to devices (eyeglasses) or treatments (eye exercises) known to improve the vision of normal persons. In diabetes, impaired eyesight is most often the result of bleeding from the retina and would not be improved by eyeglasses or such treatments.

In fact, the art cited in the present case does not even provide the basis for speculation at this level. Turning first to the Kraus article, the learning task utilized in this study is poorly described, but seems to be the effect of a delay between the presentation of a stimulus and the time in which a nondiseased dog is allowed to make its conditioned response. The Alzheimer's patient suffers from problems in language, praxis, naming, and the ability to learn new information. It is the constellation of these abnormalities that gives the Alzheimer's patient a pattern of dementia that is being regarded as relatively diagnostic. Thus, improving a small aspect of memory function in a nondiseased dog whose brain has neither the anatomical nor biochemical lesions of Alzheimer's disease is far from a valid test of a medication for Alzheimer's disease. It is not surprising that positive results from the experiments performed by Kraus are found for a class of compounds (amphetamine like) that are ineffective in Alzheimer's disease. Recently models have been established with animals with selective neurotransmitter and anatomic deficits that mimic Alzheimer's disease, that have some validity, and could be anticipated to have predictive ability. Such is not the case for this conditioned learning paradigm applied to intact animals.

Apart from galanthamine, three drugs (ethimazol, phenamine and strychnine) are referred to by Kraus as being useful in their effects on short-term memory. Ethimazol acts by increasing cAMP, a major effect of methamphetamine as well (Biull Exp Biol Med (1977) 83:185). Phenamine is methamphetamine. Methamphetamine has been directly tested in patients with Alzheimer's dementia; it has absolutely no effect (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1). Strychnine is a convulsant which stimulates brain non-

specifically (Gilman AG, Goodman LS, Rall TW, Murad F, eds., The Pharmacological Basis of Therapeutics, Macmillan Publ. Co., New York, 1985, p. 582). Pentylenetetrazol (Metrazol), a compound with convulsant and stimulant properties analogous to those of strychnine, does not improve cognitive function in Alzheimer's patients (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177). Thus, the ability of a drug to enhance memory in the experiments performed by Kraus does not indicate that the drug will be of use in Alzheimer's disease.

The teaching of the Chaplygina article does not take matters any further forward. It teaches that galanthamine reverses the amnesia-producing effects of scopolamine. However, this would be expected of an anticholinesterase. Nothing in this teaching leads to an expectation of utility against Alzheimer's disease. There are many anticholinesterase drugs available but Alzheimer's disease is still regarded as being effectively untreatable.

Applicant carried out a survey of drugs which were reported in the literature to have been useful in enhancing short-term memory over the period 1973-1976 and followed this up with a survey of whether any of them has subsequently been reported as having been tried in connection with Alzheimer's disease. The results are as follows:

39 compounds were reported to facilitate memory in various studies of animals and humans without brain lesions: adrenocorticotrophic hormone (Behav Biol (1976) 16:387, J Pharm Pharmac (1977) 29:110), ACTH 4-10 (J Pharm Pharmac (1977) 29:110, Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41, Physiol Behav (1975) 14:563, Pharmacol Biochem Behav (1974) 2:663, Physiol

Behav (1974) 13:381, Sachar EJ, ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), adenosine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), amphetamine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory MIT Press, Cambridge, Mass., 1976, p.483 Pharmacol Biochem Behav (1976) 4:703, Pharmacol Biochem Behav (1974) 2:557, Behav Biol (1977) 20:168), apovincaminate (Arzneim-Forsch (1976) 26:1947), caffeine (Acta Physiol Pharmacol Bulg (1976)2:66), desglycine lysine vasopressin (Sachar EJ, ed, Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), echinopsin (Acta Physiol Pharmacol Bulg (1976) 2:66), fluorothyl (Physiol Behav (1975) 14:151), glutamate (Brain Res (1974) 81:455), heavy water (Naturwissenschaften (1974) 61:399), histamine (Acta Physiol Pharmacol Bulg (1976) 2:49), imidazole (Acta Physiol Pharmacol Bulg (1976) 2:49), imipramine (Pharmacol Biochem Behav (1974) 2:663), isoprenaline (Pharmacol Biochem Behav (1976) 4:703), ß-lipotropin (Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41), magnesium pemoline (Behav Biol (1975) 15:245), -melanocyte stimulating hormone (J Pharm Pharmacol (1977) 29:110), methoximine (Pharmacol Biochem Behav (1976) 4:703), norepinephrine (Pharmacol Biochem Behav (1976) 4:703, Brain Res (1975) 84:329), orotic acid (Arch Int Pharmacodyn (1974) 211:123), papaverine (Acta Physiol Pharmacol Bulg (1976) 2:49), parachlorophenylalanine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), pargyline and pheniprazine (monoamine oxidase inhibitors, (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), pentylenetetrazol (Pharmacol Biochem Behav (1976) 4:123), physostigmine (Rosenzweig

MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), picrotoxin (Behav Biol (1977) 20:168), piperazine estrone sulfate (Curr Med Res Opin (1976) 4:303), piracetam (Psychopharmacology (1976) 49:307), progestagens (J Nerv Ment Dis (1976) 163:59), strychnine (Behav Biol (1977) 20:168, Arch Int Pharmacodyn (1974) 211:123), thyrotropin-releasing hormone (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1), thyroxine (J Comp Physiol Psychol (1976) 90:1082), tranylcypromine (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 508), uridine monosphate (Rosenzweig MR, Bennett EL, eds., Neural Mechanisms in Learning and Memory, MIT Press, Cambridge, Mass., 1976, p. 483), and vasopressin (Sachar EJ ed., Hormones, Behavior and Psychopathology, New York, Raven Press (1976), p. 1).

Applicant has found that of these the literature reports that ten have been tested for treatment of Alzheimer's disease. These were ACTH 4-10 (J Clin Hosp Pharmac (1985) 10:327, Neurology (1985) 35:1348), apovincaminate (J Clin Hosp Pharmac (1985) 10:327), magnesium pemoline (Lipton MA, DiMascio A, Killam KF, eds., Psychopharmacology: A Generation of Progress, Raven Press, New York, 1978, p. 1525), methylphenidate (amphetamine modified to reduce peripheral side effects (Psychopharmacology (1977) 52:251, J Am Geriat Soc 1977 25:1), monoamine oxidase inhibitors (J Am Geriat Soc 1977 25:1), papaverine (J Clin Hosp Pharmac (1985) 10:327), pentylenetetrazol (J Med Chem (1986) 29:1125, Crook T, Gershon S, eds., Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Assoc., Inc., New Canaan, Conn., 1981, p. 177.), piracetam (J Clin Hosp Pharmac (1985) 10:327, Am J

Psychiat 1981 138:593), tyrosine (increases norepinephrine, J Am Geriat Soc (1977) 25:289), vasopressin (J Clin Hosp Pharmac (1985) 10:327, J Am Geriat Soc (1977) 25:289, Neurobiology of Aging (1985) 6:95) and physostigmine as discussed above.

With the exception of physostigmine, none of these was reported to be effective in treating Alzheimer's disease.

As shown from the literature references submitted with the response, the effective treatment of Alzheimer's disease has proved to be very difficult. Many approaches have been tried. None has been successful. Galanthamine and its properties have been known for many years. No one has previously suggested that it should be used to treat Alzheimer's disease. Many drugs having similar properties to galanthamine have been tried unsuccessfully. Under these circumstances, it is quite clear that it could not possibly be obvious to one skilled in the art to use galanthamine to treat Alzheimer's disease.

In view of the foregoing, reconsideration of the 35 USC 103 rejection is respectfully requested.

Respectfully submitted,

John Richards by
Joseph H. Handelman
REG. NO. 26179

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Sullivan

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PATENT 9-24-8

MAIL ROOM SEP 11 1986 PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bonnie DAVIS

Serial No.: 819,141 Group No.: 125

Filed: January 15, 1986 Examiner: Fleisher

For: METHOD OF TREATING ALZHEIMER'S DISEASE

RECEIVED 3
SEP 17 1986
GROUP 120

Commissioner of Patents and Trademarks
Washington, D.C. 20231

PETITION AND FEE FOR EXTENSION OF TIME (37 CFR 1.136(a))

1. This is a petition for an extension of the time for a total period of two months:

(check and complete the applicable item below)

☒ to respond to the Office Letter mailed on APRIL 10, 1986

☐ for METHOD OF TREATING ALZHEIMER'S DISEASE

(Indicate matter being extended)

2. A response in connection with the matter for which this extension is requested:

☒ is filed herewith.

☐ has been filed.

3. Applicant is

☒ a small entity — verified statement:

☐ attached.

☒ already filed.

☐ other than a small entity.

4. Calculation of extension fee

	Total months requested	Fee for other than small entity	Fee for small entity
☐	one month	$ 56.00	$ 28.00
☒	two months	170.00	85.00
☐	three months	390.00	195.00
☐	four months	610.00	305.00

Fee $ 85.00

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

JOSEPH H. HANDELMAN
(Type or print name of person mailing paper)

Date: September 9, 1986

Joseph H. Handelman
(Signature of person mailing paper)

1 216 85.00 CK

819141

(check and complete the next item, if applicable)

☐ An extension for _____ months has already been secured and the fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $_____

8. Fee Payment

☒ Attached is a check in the sum of $ 85.00

☐ Charge fee to Account No. _____ and for any additional extension fee required or credit for any excess fee paid. A duplicate of this petition is attached.

JOHN RICHARDS
c/o LADAS & PARRY
26 WEST 61st STREET
NEW YORK, N.Y. 10023
Reg. No. 31053 (212) 708-1915

John Richards by Joseph H. Handelman REG. NO. 26179

Reg. No.:

Tel. No.: ( )

SIGNATURE OF ATTORNEY
JOHN RICHARDS

Type or print name of attorney

P.O. Address

UNITED STATE PARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	5

DATE MAILED:

NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to 9/11/86
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☐ The allowed claims are 1-7.
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [__] been received. [__] not been received. [__] been filed in parent application Serial No. _____, filed on _____
6. ☐ Note the attached Examiner's Amendment.
7. ☐ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☒ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- Examiner's Amendment
- Examiner Interview Summary Record, PTOL-413
- Reasons for Allowance
- ☒ Notice of References Cited, PTO-892
- Information Disclosure Citation, PTO-1449
- Notice of Informal Application, PTO-152
- Notice re Patent Drawings, PTO-948
- Listing of Bonded Draftsmen
- Other

Stanley J. Friedman
Primary Examiner
Group Art Unit 12

PTO-37 (REV. 3-85)

USCOMM-DC 45-3744

OL-85 (Rev. 5-85)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

LESTER HORWITZ
C/O LADAS & PARRY
26 WEST 61ST STREET
NEW YORK, NY 10023

All communications regarding this application should give the serial number, date of filing, name of applicant, and batch number.

Please direct all communications to the Attention of "OFFICE OF PUBLICATIONS" unless advised to the contrary.

The application identified below has been examined and found allowable for issuance of Letters Patent. PROSECUTION ON THE MERITS IS CLOSED.

SC/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
06/819,141	01/15/86	007	FRIEDMAN, S	125	10/30/86

st med plicant	DAVIS,	BONNIE

LE OF ENTION: METHOD OF TREATING ALZHEIMER'S DISEASE

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
U 5631	514-215.000	727	UTILITY	YES	$200.00	01/20/87

The amount of the issue fee is specified by 37 C.F.R. 1.18 as follows: for an original or reissue patent, except for a design or plant patent, $500; for a design patent, $175; and for a plant patent, $250. If the applicant qualifies for and has filed a verified statement of small entity status in accordance with 37 C.F.R. 1.27, the issue fee is one-half the respective amount aforementioned. The issue fee due printed above reflects applicant's status as of the time of mailing this notice. A verified statement of small entity status may be filed prior to or with payment of the issue fee. However, in accordance with 37 C.F.R. 1.28, failure to establish status as a small entity prior to or with payment of the issue fee precludes payment of the issue fee in the amount so established for small entities and precludes a refund of any portion thereof paid prior to establishing status as a small entity.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE as indicated above. The application shall otherwise be regarded as ABANDONED. The issue fee will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the Patent and Trademark Office. Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of the notice of allowance, the issue fee is charged to the deposit account at the time of mailing of this notice in accordance with 37 C.F.R. 1.311. If the issue fee has been so charged, it is indicated above.

In order to minimize delays in the issuance of a patent based on this application, this Notice may have been mailed prior to completion of final processing. The nature and/or extent of the remaining revision or processing requirements may cause slight delays of the patent. In addition, if prosecution is to be reopened, this Notice of Allowance will be vacated and the appropriate Office action will follow in due course. If the issue fee has already been paid and prosecution is reopened, the applicant may request a refund or request that the fee be credited to a Deposit Account. However, applicant may wait until the application is either found allowable or held abandoned. If allowed, upon receipt of a new Notice of Allowance, applicant may request that the previously submitted issue fee be applied. If abandoned, applicant may request refund or credit to a Deposit Account.

In the case of each patent issuing without an assignment, the complete post office address of the inventor(s) will be printed in the patent heading and in the Official Gazette. If the inventor's address is now different from the address which appears in the application, please fill in the information in the spaces provided on PTOL-85b enclosed. If there are address changes for more than two inventors, enter the additional addresses on the reverse side of the PTOL-85b.

The appropriate spaces in the ASSIGNMENT DATA section of PTOL-85b must be completed in all cases. If it is desired to have the patent issue to an assignee, an assignment must have been previously submitted to the Patent and Trademark Office or must be submitted not later than the date of payment of the issue fee as required by 37 C.F.R. 1.334. Where there is an assignment, the assignee's name and address must be provided on the PTOL-85b to ensure its inclusion in the printed patent.

Advance orders for 10 or more printed copies of the prospective patent can be made by completing the information in Section 4 of PTOL-85b and submitting payment therewith. If use of a Deposit Account is being authorized for payment, PTOL-85c should also be forwarded. The order must be for at least 10 copies and must accompany the issue fee. The copies ordered will be sent only to the address specified in section 1 or 1A of PTOL-85b.

☑ Note attached communication from Examiner.

☐ This notice is issued in view of applicant's communication filed _____

IMPORTANT REMINDER

Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. See 37 CFR 1.20 (e)–(j).

TO SEPARATE, REMOVE TOP AND BOTTOM EDGES. SNAP –APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	819,141	125	5
	APPLICANT(S) DAVIS		

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
A						
B						
C						
D						
E						
F						
G						
H						
I						
J						
K						

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG.	PERTINENT PP. SPEC.
L								
M								
N								
O								
P								
Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

X R Hashenson et al. J. Med. Chem. Vol. 29, No. 7 7/86 pp. 1125 – 1130

X S Kendall et al., J. Chem. Hospital Pharmacy. (1985) 10 – 327-336

X T S. Chaplygina et al., J. of Higher Nervous Activity Vol. XXIV: 1976 Issue 5 pp. 1–4

X U Krause, J. of Higher Nervous Activity, Vol XXII 1974 Issue 1

EXAMINER	DATE
Friedman	9/26/88

*A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

Journal of Medicinal Chemistry

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Perspective

Drug Development for Senile Cognitive Decline

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Received February 17, 1986

Introduction. The treatment of senile[1] cognitive decline is one of the greatest challenges in the health sciences today. No truly effective therapy has yet been launched; thus research in the cognitive sciences has the potential to produce enormous medical benefits. For the many scientists working to find a cognition activator with robust effects, the risk lies in the possibility that senile cognitive decline may not be treatable. In this paper, we hope to bring relevant data on senile cognitive decline into a meaningful relationship, thus providing a functional perspective for further research. Readers are reminded that this is a Perspective, not a Review. More comprehensive accounts can be found in the recent literature.[2,3]

Dementia is a clinical syndrome involving reduced intellectual functioning with impairments in memory, language, visuospatial skills, and cognition (including mathematics, abstraction, and judgment).[4] Currently, several dementias can be treated (Table I), but others cannot, most notably primary degenerative dementia (PDD; also called senile dementia, senile dementia of the Alzheimer type, Alzheimer disease, organic brain syndrome).

Many health problems contribute to senile cognitive decline, including PDD, mild (or minimal) memory impairment (also called benign senescent forgetfulness), and multiinfarct dementia. The most common accepted form of senile cognitive decline is PDD. *While better drugs are still needed for treatable dementias, untreatable cognitive disorders, particularly PDD, present the greatest challenges and will be the focus of this Perspective.*

Table I. Treatable Dementias[5]

intracranial conditions
multiinfarct dementia (MID)
extrapyramidal disorders (EPS)
hydrocephalus
subdural hematomas
intracranial neoplasms
infections
chemical intoxications
drugs
metals
industrial waste
depression
systemic disorders
cardiovascular
hepatic
endocrine
renal
nutritional deficiencies
collagen-vascular diseases

The original diagnosis of PDD was made in 1907 by Alois Alzheimer.[6] Alzheimer reported on a 56-year-old woman who had died following a 5–6-year illness characterized by personality changes, disorientation, and memory loss. Postmortem microscopic examination of brain tissue taken from this patient revealed high densities of lesions that are currently described as neuritic plaques and neurofibrillatory tangles. The microscopic changes had previously been observed only in the brains of people over 70 years of age; however, the relationship between normal aging of the brain and PDD remains unresolved.[7]

PDD was considered a medical curiosity for many years; however, the magnitude of its occurrence, especially in the elderly, has only been appreciated within the past decade. Data from population studies suggest a 10- to 20-fold in-

(1) The term "senile", per se, refers only to old age, not to a mental disorder. We will use the phrase "senile cognitive decline" to denote the variety of cognitive disorders observed in the elderly.

(2) See, for example, Busby, J.; Bonelli, A.; Vargas, L.; Stirna, J.; Caranasos, G. *J. Am. Geriatr. Soc.* 1985, *33*, 366. Blass, J. P. *Disease-a-Month* 1985, *31*, 1. Hutton, J. T.; Kenny, A. D., Eds. *Senile Dementia of the Alzheimer Type*; Alan R. Liss: New York, 1985.

(3) A particularly good collection of articles on Alzheimer disease and related disorders can be found in Roth, M.; Iversen, L. L., Eds. *Br. Med. Bull.* 1986, *42* (1).

(4) Cummings, J.; Benson, D. F.; LoVerme, S., Jr. *J. Am. Med. Assoc.* 1980, *243*, 2434. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed.; American Psychiatric Association: Washington, DC, 1980 (commonly referred to as DSM-III). For suggested improvements to DSM-III, see, for example, Jorm, A. F.; Henderson, A. S. *Br. J. Psychiatry* 1985, *147*, 394.

(5) Cummings, J. L. *Clin. Ther.* 1985, *7*, 480.

(6) For a translation of the original report, see Wilkins, R. H.; Brody, I. A. *Arch. Neurol.* 1969, *21*, 109.

(7) A review of the biochemical characteristics of PDD is beyond the scope of this article. For reviews, see, for example, Thienhaus, O. J.; Hartford, J. T.; Skelly, M. F.; Bosmann, H. B. *J. Am. Geriatr. Soc.* 1985, *33*, 715. Gottfries, C. G. *Psychopharmacology* 1985, *86*, 245. Rathmann, K. L.; Conner, C. S. *Drug Intell. Clin. Pharm.* 1984, *18*, 684. Price, D. L.; Kitt, C. A.; Struble, R. G.; Whitehouse, P. J.; Cork, L. C.; Walker, L. C. *Ann. N.Y. Acad. Sci.* 1985, *457*, 35.

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crease in the prevalence of PDD between ages 60 and 80, and the incidence of PDD will increase in the coming years as the geriatric segment of the population grows. In the United States alone, the segment of the population presently over 65 is estimated at 11% or 25 million people. Over the next 50 years this figure should grow to 55 million or 20% of the population.[8]

The scientific study of PDD has been hampered by (1) the lack of an early, reliable diagnostic method, (2) an unknown etiology, (3) little knowledge about the homogeneity or heterogeneity of the disease,[9] and (4) the absence of effective therapeutic agents and appropriate animal models.

The onset of PDD is insidious, usually taking several years before either the affected individual or close family members recognize that a medical problem may exist. The earliest symptom is forgetfulness (e.g., recent events, names of individuals, locations of objects). While the patient manages daily activities during the early phase of PDD, routine tasks become increasingly difficult as the disease progresses. The patient becomes disoriented, confused, and experiences emotional changes, most frequently those of depression. Occasionally, hallucinations accompany the behavioral changes. In the final stages of PDD, neurological functions fail, and the ability to move and communicate is eventually lost. A Global Deterioration Scale has been developed to categorize the severity of the disease based on behavioral characteristics.[10] PDD is most frequently observed in individuals over age 50, and while the progression of the disease is somewhat variable, it is usually faster when the onset occurs at an earlier age.

Diagnosis. Primary degenerative dementia is currently diagnosed by excluding other possible causes of the observed behavioral manifestations. Neuropsychological tests, including the mini-mental status questionnaire[11] and the behavioral test of Blessed[12] are used to assess the degree of dementia. Other possible causes, including those mentioned above (Table I), are excluded on the basis of clinical history or laboratory data. For example, multiinfarct dementia, the second most common form of dementia, is excluded by using Hachinski criteria,[13] and laboratory examination of blood and urine samples is used to rule out factors such as vitamin B_{12} deficiency or drug intoxication.

Unfortunately, no objective, unequivocal diagnostic procedure is presently available for early detection of PDD or quantification of cognitive decline. New imaging techniques such as positron emission tomography[14] and magnetic resonance may provide insights into differences in brain functioning between PDD patients and age-matched controls; however, these methods are not yet suited for evaluating large numbers of patients routinely. Other laboratory measures involving multichannel computer-analyzed electroencephalography (EEG), cerebral blood flow monitoring,[15] computerized tomography of brain mass, and analysis of cerebrospinal fluid may provide useful markers that are more easily obtained and quantified. PDD patients may display greater sensitivity to certain pharmacological agents (e.g., the anticholinergic scopolamine) than normals, thus allowing a more accurate assessment of their disorder.[16] Evoked potential recording may be of value in diagnosing early PDD.[17] Other differences may eventually be exploited (e.g., fingerprint patterns,[18] hyperammoniemia[19]); however, much research must be done before such methods can be established as valid diagnostic tools. Success in developing rapid and reliable diagnostic procedures will ultimately play an important role in the clinical development of new therapeutic agents.

Table II. Possible Causes of PDD[20]

genetic factors
abnormal protein models
infectious agents
toxins
blood flow disorders
cholinergic hypothesis
multiple factors

Etiology. The etiology and pathogenesis of PDD is presently unclear; however, a number of factors have been hypothesized to be involved (see Table II). Questions exist whether PDD is a single entity or two disorders; one with an onset before age 65 (presenile dementia), and a second with symptoms appearing in later life (senile dementia). This issue has not been resolved.

The possibility that PDD can be inherited has been a subject of interest for some time. Results from several studies suggest a genetic predisposition to PDD, especially in cases of early onset.[21] Close relatives of PDD patients have a fourfold greater chance of developing the disease than the general population.[22]

Recently, the possibility that chromosoinal abnormalities may be involved in the etiology of the disease has been proposed because many individuals with Down's syndrome who reach age 40 develop Alzheimer-type brain lesions and clinical dementia.[23] Additionally, PDD and Down's syndrome share a unique cerebrovascular amyloid fibril protein.[24]

Evidence suggesting that PDD is an infectious disease, possibly of viral origin, is based on certain clinical and neuropathological similarities between PDD and Creutz-

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(23) Price, D. L.; Whitehouse, P. J.; Struble, R. G. *Ann. N.Y. Acad. Sci.* 1982, *396*, 145. Cutler, N. R.; Heston, L. L.; Davies, P.; Haxby, J. V.; Schapiro, M. B. *Ann. Internal Med.* 1985, *103*, 566. Masters, C. L.; Simms, G.; Weinman, N. A.; Multhaup, G.; McDonald, B. L.; Beyreuther, K. *Proc. Natl. Acad. Sci. U.S.A.* 1985, *82*, 4245.
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feldt–Jakob disease (CJD). CJD is a rare disorder of progressive dementia accompanied by movement disturbances that is followed by death within 1–2 years from onset. The infectious agent may be a slow virus because an incubation period of several years is required between exposure to the agent and the first symptoms. Scrapie, a brain disorder of sheep and goats, is an infectious disease that may also involve slow viruses. Both can be transmitted by injecting extracts of infected brain tissue.

Prusiner and co-workers have recently demonstrated the infectious pathogen in scrapie to be a protein particle termed a prion.[25] Prions are defined as small, proteinaceous, infectious particles that resist inactivation by procedures that modify nucleic acids. All attempts to demonstrate the existence of nucleic acids within the scrapie agent have failed—how such proteins replicate without genetic material has not been satisfactorily answered.

The rodlike structures observed upon microscopic examination of sheep brains infected with scrapie are thought to be prion aggregates, but these aggregates are not the same as the neuritic plaques seen in PDD.

The transmission of PDD from human brain tissue to experimental animals has not been successful. Establishment of suitable animal models reflecting an infectious type of PDD may be confounded by excessively long incubation periods that exceed the animal's normal life span.

If an infectious agent like a slow virus or a scrapie-like prion is involved in PDD, other factors may be required before the disease can be fully manifested. These may include a genetic predisposition, as mentioned above, or exposure to environmental toxins. Changes in the blood–brain barrier may occur in PDD, thereby causing an increased permeability of the microvasculature that contributes to the observed pathology.[26]

Neurochemical analysis of neuritic plaques is another area of active research. Whether plaques are end products of the pathological process or simply contributors to the disease is not known. Nevertheless, an understanding of the chemical nature of these morphological markers may provide direction in designing new therapeutic agents. Cholinergic, catecholaminergic, and somatostatinergic processes are present in plaques along with proteinaceous material (amyloid).[27] Amyloid is also found in cerebral blood vessels, and leakage of amyloid from vessels into brain tissue has been postulated to trigger the neurotoxicity observed in PDD.[22] Amyloid may originate from a blood-borne precursor protein, being formed in cerebral blood vessels by action of a local enzyme.

The presence of elevated aluminum levels in the brain tissue of PDD patients was originally used to suggest this metal as a causative factor in the disease.[28] While comparisons of brain aluminum levels in PDD patients vs. age-matched controls show little difference,[29] an inorganic substance composed of aluminum and silicon is present in the plaques found in PDD.[28] This remains a controversial area because patients suffering from aluminum toxicity do not exhibit the neuropathological changes characteristic of PDD.[30]

Recent studies involving nerve growth factors suggest a possible new direction for research on the etiology of senile cognitive decline, but more work is needed.[31]

Finally, the function of the immune system[32] in the pathogenesis of PDD is under intense study, but conclusions at this time would be premature. For example, conflicting reports[33,34] have appeared regarding the correlation of levels of serum immunoglobulins A and G with the degree of cognitive impairment in PDD. A genetic factor may be responsible for changes in the immune system of PDD patients.

Past Strategies. The drugs currently used in the treatment of PDD are of questionable value. The earliest therapeutic strategies used agents that improve cerebral blood flow or are mild psychostimulants. In the United States, dihydroergotoxine, the vasodilators papaverine, isoxsuprine, and cyclandelate, and the stimulants methylphenidate and pentylenetetrazole, have been approved for the treatment of senile cognitive decline.[35] Dihydroergotoxine, a mixture of three dihydrogenated ergot alkaloids, is the most widely used drug of this group. *None of these agents has been demonstrated to improve cognition unequivocally in PDD patients.*

Compounds that improve cerebral blood flow through vascular mechanisms have been employed in some countries to treat PDD. These compounds include naftidofuryl, pentoxifylline, suloctodil, vincamine, and calcium channel blockers (e.g., nimodipine). The use of these agents is debatable since a vascular origin for PDD is no longer widely accepted.

A group of agents termed nootropics have been developed on the basis of the observation that the pyrrolidone piracetam facilitates learning and memory in animal models. Human studies with piracetam continue to give conflicting results. Several compounds appear to be more potent than piracetam and have been evaluated clinically in patients with cognitive decline (see Table III).[36] Initial reports from open-label studies have often been encouraging, but well-designed, double-blind, placebo-controlled trials have thus far failed to confirm clear-cut drug effects.

Present Strategies. The focus of research has now shifted to biochemical and neurochemical approaches, with the hope of identifying agents that improve the behavioral endpoints of learning and memory by a defined mechanism of action. Present strategies include cholinergic agents

Table III. Representative Nootropics

piracetam
oxiracetam
pramiracetam (CI-879)
rolziracetam (CI-911)
aniracetam
CI-933
CI-844

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(36) See references cited in *Drugs Future* 1985, *10*, 972, 988.

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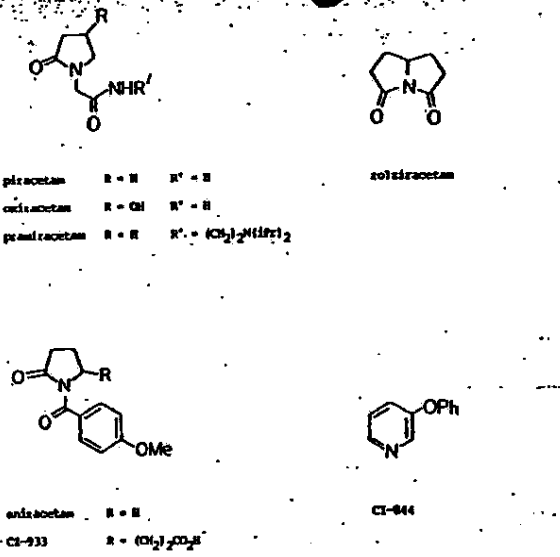


(e.g., arecoline,[37,38] physostigmine,[38] RS-86,[39] bethanecol,[40] BM-5[41]), analogues of ACTH (e.g., ORG 2766[42]), vasopressin (e.g., DDAVP[43], DGAVP[44]), and somatostatin (e.g., L-363,586[45]), serotonin agents (e.g., alaproclate[46], zimelidine[47]), and adrenergic agents (e.g., clonidine[48]). The most widely accepted biochemical hypothesis, at present, involves the cholinergic system, which is discussed in more detail below.

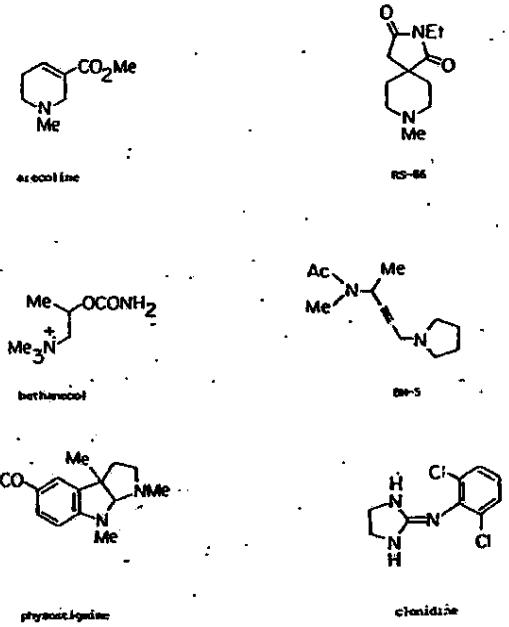
Table IV. Agents That May Enhance Muscarinic Neurotransmission in Diseases Characterized by a Muscarinic Cholinergic Deficiency[a]

class	example[b]
presynaptic muscarinic antagonist	scopolamine
presynaptic allosteric muscarinic inhibitor	gallamine
presynaptic enhancer of acetylcholine release	aminopyridines
enhancer of high affinity choline uptake	?
reversible inhibitor of acetylcholinesterase	physostigmine
postsynaptic muscarinic agonist	arecoline, oxotremorine
postsynaptic allosteric muscarinic activator	?

[a] None of these appear to be selective for pre- or postsynaptic sites. However, see ref 41 (BM-5).

Table V. Correlation between Electroencephalography and Behavior

EEG band	behavior
alpha (8–12 Hz)	attentional demands
beta (16–24 Hz)	emotion, cognition
theta (2–7 Hz)	cognition (particularly hippocampal theta)



Biological Models. In order to develop new therapeutic agents in a rational and efficient manner, satisfactory biological models are needed. *Unfortunately, appropriate animal models do not yet exist.* Many considerations are important in developing effective animal models. For example, the animal model should be sensitive and selective for certain types of memory, and confirmation that memory is required in normal animals for accurate performance is essential. The performance of animals with altered brain function should be comparable to similar modulation of human memory. Finally, nonmemory psychological processes must be excluded as possible causes of behavioral changes.

The validity of animal models of cognition is ultimately tested by their ability to predict or at least explain brain mechanisms involved in normal memory, pathological changes that produce memory impairments, and thera-

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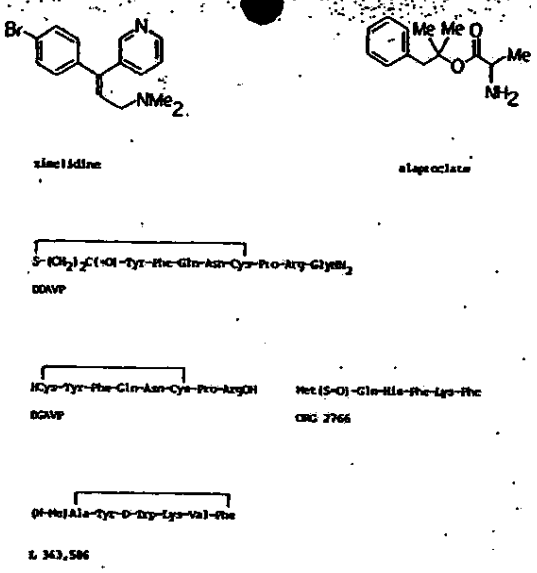

peutic interventions that alleviate memory impairments.

For the purposes of discussion, biological models of senile cognitive decline will be divided into three major neuropharmacological categories: biochemistry, electrophysiology, and behavior. The past generation of cognition activators was developed almost entirely through leads discovered during the course of behavioral testing. The present generation of agents represents a shift to better defined mechanisms of action wherein leads are identified through combined evaluation in all three areas of neuropharmacology.

For example, consider the cholinergic hypothesis, which has been proposed to explain the pathology and symptoms of geriatric memory dysfunction.[49] An impressive amount of research has been directed by this rationale in the 1980s.[50] If indeed the cholinergic deficits observed in PDD cause the cognitive decline observed, then, in principle, symptomatic treatment should be possible with several types of cholinergic agents. (However, activation of just one neurotransmitter system may not be enough to overcome the symptoms associated with PDD.)

Mechanistic questions are best addressed at an early stage through biochemical studies because of high testing throughput and minimal complicating pharmacokinetic and metabolic factors. In a cholinergic approach, these investigations might include a variety of assays: muscarinic receptor binding, high-affinity choline uptake, acetylcholine release, choline acetyltransferase activity, acetylcholinesterase activity, phosphatidylinositol turnover.

These assays can provide primary mechanistic models of senile cognitive decline. Alone, their value is limited, but in tandem with electrophysiology and behavioral testing, biochemical studies serve to provide rapid, well-defined input regarding potential activity, thus directing more time consuming efforts efficiently. Examples of agents that may enhance muscarinic cholinergic neuro-

Table VI. Behavioral Models

central nervous system (CNS) lesions
electrical (e.g., electroconvulsive shock (ECS))
genetic deficiencies
hypoxia/anoxia and ischemia
aged vs. young animals
drug-induced deficits

transmission by a defined biochemical mechanism are illustrated in Table IV.

Brain electrical activity can be studied with standard electroencephalographic equipment. Coupled with behavioral studies, certain electrical changes have been correlated with attentional demands, emotional processes, and cognitive processes,[51] as outlined in Table V. Through this correlation, electrophysiology functions as a secondary mechanistic model for senile cognitive decline, and can serve in addition to provide information on duration of action, time course, time of peak effect, and potential toxicity.

Behavioral studies represent the penultimate endpoint in the development of drugs to treat senile cognitive decline, and a number of behavioral models exist at the present time (see Table VI). The discussion that follows summarizes and updates some recent reviews on this subject.[52]

CNS Lesions. Studies of biochemical and histopathological changes in PDD patients, particularly in the cholinergic system, have suggested new approaches to developing animal models of senile cognitive decline. Ventral pallidal lesions produced by ibotenic acid do not alter rat performance on psychomotor tasks or affect sensitivity to shock.[53] However, severe deficits in retention of a passive avoidance response are found in these lesioned animals. Similar deficits are found in rats lesioned bilaterally in the ventral pallidum with use of another excitatory neurotoxin, kainic acid. Ethylcholine mustard aziridinium ion (AF64A), a neurotoxic choline analogue, produces long-lasting hypofunction of central cholinergic systems in mice and reduces presynaptic cholinergic markers in the rat hippocampus without affecting postsynaptic muscarinic receptor binding.[54] AF64A lesions may eventually provide an animal model of PDD, but behavioral evidence is preliminary. The use of cholinergic false precursors has also been suggested as a method for producing animals with cholinergic hypofunction.[55]

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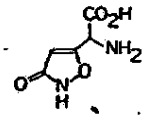
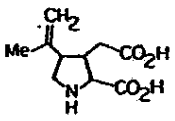
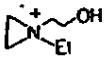
(54) Vickroy, T. W.; Watson, M.; Leventer, S. M.; Roeske, W. R.; Hanin, I.; Yamamura, H. I. *J. Pharmacol. Exp. Ther.* 1985, *235*, 571. Fisher, A.; Mantione, C. R.; Abraham, D. J.; Hanin, I. *J. Pharmacol. Exp. Ther.* 1982, *222*, 140. Swertka, S. A.; Olton, G. L. *Life Sci.* 1986, *38*, 1105. An aziridinium analogue of oxotremorine (BM130A) has also been studied (Russell, R. W.; Crocker, A. D.; Booth, R. A.; Jenden, D. J. *Psychopharmacology* 1986, *88*, 24).



ibotenic acid



kainic acid



AF-64A

ECS Models. Electroconvulsive shock has been used to produce severe retrograde amnesia, an effect well-documented at the clinical level and extensively studied in animals. The effects of agents on impaired memory in depressed patients undergoing ECS therapy are under study.[56] Since many cognition activators were discovered and developed on the basis of activity against ECS-induced amnesia, these studies will test the predictive value of this preclinical model.

Genetic Models. Natural deficits can be observed in certain genetic strains. For example, hippocampally deficient mice[57] are impaired in acquisition and retention with regard to finding a hidden platform in a water "maze".

Hypoxia Models. Low levels of oxygen induce electrophysiological changes and disrupt learning and memory. Even certain biochemical effects caused by hypoxia parallel those seen in aging. For example, treatment of spontaneously hypertensive rats with hypertonic saline causes behavioral deficits, and a morphology similar to that observed in multiinfarct dementia.

Aged Models. Old animals are used extensively as models of age-related cognitive disorders. Regional changes in brain glucose metabolism reflect cognitive impairments in aged rats.[58] Old mice are impaired on passive avoidance compared to young mice. In contrast with clinical data, dietary phosphatidylcholine enhances performance of old mice in shuttlebox avoidance. Aged rats perform at chance levels after 15 training trials using a 12-arm radial maze, whereas young rats master the task. Positive correlations in aged rats have been found between maze performance and hippocampal choline acetyltransferase activity. Aged monkeys have been employed in studies of age-related memory impairments and drug effects upon memory. Drug trials in monkeys have demonstrated effects with cholinergic agents and neuropeptides similar (i.e., marginal efficacy) to those reported in human trials.

Drug-Induced Deficit Models. Anticholinergic-induced cognitive deficits have also been used as a model of age-related impairments, with agents tested for their ability to reverse the deficits. Systemically administered atropine increases running time and working memory errors in mice trained on a six-arm radial maze. In a water maze, atropine-treated rats are impaired with respect to finding a hidden escape platform. Similar deficits are found in rats with total hippocampalectomy. Atropine disrupts and physostigmine enhances acquisition of light/dark discrimination and tone/no-tone discrimination in rats. Anticholinergics are also effective in disrupting memory when injected directly into the brain. Conversely, cholinergic agents (e.g., arecoline, physostigmine, oxotremorine, muscarine) improve retention on an active avoidance task when administered intracerebroventricularly after training and prior to retention testing 1 week later. MCI-2016 [4-(*o*-benzylphenoxy)-*N*-methylbutylamine] reverses scopolamine-induced impairments of spontaneous alternation responding in rats similar to the effects of physostigmine, choline, and amphetamine.

Benzodiazepine-induced amnesia, which was first described as a result of clinical experience, has been used as an animal model of amnesia.[59]

Are the Models Valid? *An unequivocal answer to this question may not be possible until a truly efficacious drug is discovered, thus allowing a comparison of preclinical and clinical results.* However, given a variety of agents that show some preclinical activity, the following scenarios pertain. (1) Perhaps the models are valid, but greater preclinical efficacy is needed. In this case we should seek drugs with more robust preclinical effects. (2) Perhaps side effects, a short duration of action, or a narrow active dose range mask the efficacy of useful drugs. Here, agents with fewer side effects, longer duration, and wider active dose ranges are needed. (3) Perhaps patient populations have been inadequately selected for clinical evaluation. If this is true, then we must develop means of accurately diagnosing varied types of senile cognitive decline, for example, with imaging techniques. (4) Perhaps the clinical symptoms of senile cognitive decline cannot be treated with drugs. If this is true, then efforts might be focused on prevention of senile cognitive decline or on surgical intervention, for example, with brain tissue transplants.[60]

Future Directions. The cognition activators currently under development are a diverse group. Whether these agents prove effective remains to be seen. Future cognition activators should not only act via defined mechanisms but should also possess undisputed efficacy. Whether the next generation arises from a series of incremental advances or a significant breakthrough, a major new era in neurosciences will be ushered in.

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REVIEW ARTICLES

THERAPEUTIC PROGRESS—REVIEW XVIII ALZHEIMER'S DISEASE

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INTRODUCTION

In the Western world an increasing proportion of the population is elderly. By the year 1995, 1·76 million people in England and Wales will be over 80 years of age (1). It is estimated that 20% of the population over 80 suffer with dementia in one form or another. The problem is therefore large, and likely to become enormous in the next 10 years. There are a number of causes of dementia and the main ones are set out in Table 1. However, most demented patients are suffering from either multi-infarct dementia, Alzheimer's Disease or a combination of the two. Alzheimer's Disease or Dementia Alzheimer-type (DAT), which is responsible for most cases, is characterized by diffuse cerebral atrophy and enlargement of ventricles, accompanied by large numbers of senile plaques, Alzheimer's neurofibrillary tangles and granulovacuolar degeneration. Clinical presentation is mainly with impairment of memory, deterioration in intellectual function and change in personality and behaviour (2). Depression may occur secondary to these changes and focal neurological signs may be observed. 'Pseudodementia' due to severe depression, drugs and other neurological causes of dementia (see Table 1) should be excluded. The cause of DAT is unknown, although it is possible that a neuropharmacological deficit may be contributing to its manifestations.

There is no adequate treatment of DAT at the present time, although there are a very large number of drugs which are being used in the hope of achieving some kind of benefit. The uncertainty about the cause, the large number of patients involved, and the vast array of potential medications available make the investigation into the treatment of Alzheimer's Disease one of the most important challenges in therapeutics today.

The aim of this review is to present an assessment of the drug treatment of dementia accepting that this is only part of the management of patients with Alzheimer's disease. The non-pharmacological measures which are designed to assist the patient and the relatives cope with a prolonged, debilitating, terminal illness are very important but will not be discussed further in this review.

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In addition, apparent improvements in a patient's pattern of life, brought about by symptomatic therapy, should not be attributed to control or reversal of the basic disease process. Unless care is taken, drugs may be thought to have therapeutic properties whereas in reality they are producing marginal symptomatic improvements not associated with any intellectual change.

'Therapeutic' treatment

The word therapeutic is written in quotes to emphasize the fact that no form of treatment has yet been shown to improve the basic disease process in Alzheimer's disease. However, some recent advances have yielded encouraging results making optimism more appropriate than nihilism in this difficult therapeutic area.

The possibility that Alzheimer's disease is caused by a neuropharmacological defect, probably in the cholinergic system, and the therapeutic implications of this, are particularly exciting. These will be discussed in the next section. The other agents and the problems associated with assessing their efficacy, or lack of it, are considered in the subsequent section.

THE CHOLINERGIC SYSTEM

Three ways of trying to correct the adverse consequences of cerebral acetylcholine deficiency have been suggested and tried: (a) to increase the availability of suitable precursors, (b) to decrease the breakdown of the acetylcholine and (c) to supplement the effects of acetylcholine by administering other cholinomimetic agents.

Precursors

Precursors have been given in the, perhaps mistaken, belief that by providing an excess of substrate the deficiency of acetylcholine can be corrected. To be effective, the material administered by mouth would have to be absorbed to attain sufficient concentrations, first in the blood and thereafter in the central nervous system, and not cause any adverse effects. The enzyme system in the brain would then have to be able to utilize the chemical provided. In the hope that this may be possible, various salts of choline, lecithin (phosphatidylcholine) and deanol (2-dimethylamino-ethanol) have been given to groups of patients with Alzheimer's disease.

Choline has been assessed by a number of different investigators (3, 4). As with most treatments for Alzheimer's disease the trials can be criticized. Usually the substance is given to a small group of patients for a short time and assessed without using a double-blind technique. Although animal studies suggest that brain concentrations of choline can be increased, the clinical data which are available do not suggest that choline has any useful therapeutic effect (3, 4); though the trials could not be said to prove that choline is ineffective. It produces a fishy odour and gastrointestinal upsets.

Lecithin, which is rapidly converted into choline (4), is difficult to obtain in a pure form and is expensive. Nevertheless, this substance has been investigated more extensively than choline. The overall impression, however, is one of disappointment (4, 5, 6, 7) though again the lack of efficacy could be ascribed, to some extent, to the inadequacy of the trials. One longer study, using larger doses of lecithin, yielded

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Table 1. Causes of dementia (an abbreviated list)

Primary	Alzheimer's Disease
	Pick's Disease
	Huntington's chorea
	Creutzfeld–Jakob Disease
Secondary	
Vascular	Multi infarct dementia
Trauma	Head injuries
	Subdural haematoma
Anoxia	Cardiac failure
Metabolic	Hypothyroidism
	Hypercalaemia
	Cushing's Disease
	Dialysis dementia
	Hepatic encephalopathy
Nutritional	Vitamin deficiencies (e.g. folic acid or B12)
Altered CSF dynamics	Hydrocephalus
Space occupying lesions	Tumours, metastases
Infections	Meningitis or encephalitis
Drugs	C.N.S. depressing agents

SUPPORTIVE, SYMPTOMATIC AND 'THERAPEUTIC' TREATMENT

Alzheimer's disease tends to occur in late middle age or in the elderly, and it is possible to use drugs to assist patients in three quite different ways. Supportive therapy is that which is given to correct any defects which may be contributing to the patient's poor condition. Symptomatic therapy is given in an attempt to control associated symptoms such as anxiety, insomnia and depression which are a reaction to the dementing illness. 'Therapeutic' treatment implies that the intention is to rectify the cause or one of the basic defects of the disease.

Supportive treatment

The clinical condition of a patient with Alzheimer's disease will be made worse if there are coexisting disorders. Parkinson's disease, deafness, infections and malnutrition are all potentially treatable. These conditions must be detected and treated.

Symptomatic treatment

The essential clinical manifestations of Alzheimer's disease are a loss of intellectual function and memory which may progress to an extent that precludes independent existence. This may lead to distress, confusion, aggresive behaviour, insomnia, depression and loss of interest in personal hygiene. These may, to some extent, be amenable to appropriate drug treatment, and are particularly important to those who care for the patients at home or the staff of an institution. However, it is important to approach the control of symptoms rather cautiously since sedation may increase the confusion and further impair memory, thereby making the clinical condition worse.

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some more promising early results (8) but evidence of long-term, clinically relevant improvement is lacking.

The third precursor which has been the subject of a number of investigations is deanol. The literature on this agent contains a number of papers based on small groups of patients using open techniques which show some improvements in one or more measures of cognitive function or behaviour (9, 10). In more carefully controlled investigations, of greater duration, it seems that adverse effects can be a problem, particularly as the dose is increased and evidence of an overall improvement is not found (11).

Anticholinesterases

Many anticholinesterases are toxic, short-acting and do not pass readily across the blood–brain barrier. It would seem, at first sight, therefore, that treatment with these agents would require a complicated regimen with considerable risk of producing adverse effects. However, the theoretical possibility of developing a long-acting preparation of an agent with good brain penetration, and possibly some selectivity of action towards the relevant cortical cholinergic system, must be seen as a major challenge for researchers working on Alzheimer's disease.

Physostigmine does penetrate into the central nervous system and early trials with this drug have yielded some encouraging results. Whereas anticholinergic agents may cause an impairment of recognition memory function, physostigmine, given intravenously, has been shown to produce an improvement both in normal subjects (12) and in patients with Alzheimer's disease (13). The demonstration of a dose-response effect is intellectually satisfying, since this is what one would predict if a defect is being corrected pharmacologically. It is also of interest that, the combination of lecithin with physostigmine appeared to be preferable to physostigmine alone, in a small group of patients with Alzheimer's disease (14).

Having established that parenteral physostigmine may have a role in improving memory function, in both controls and demented patients, the next step was to assess the effects of orally administered physostigmine. Thal and Fuld (15), after performing a dose finding study, have shown that 8 of 12 patients, given oral physostigmine with lecithin, did appear to improve. Similarly Davis and colleagues (16), also after determining the optimal dose, have demonstrated an improvement using a double-blind technique in a small group of patients with Alzheimer's disease who were given oral physostigmine alone.

Although we are a long way from curing or preventing Alzheimer's disease, the apparent beneficial effects of modifying and trying to correct one of the systems, thought to be defective, is an encouraging observation in an area of therapeutic uncertainty.

Cholinomimetic agents

An increased effect on cholinergic receptors could also be achieved by the administration of muscarinic agonists. Agents like arecholine have been tried and may produce modest improvements in learning and memory but the problem of systemic side-effects, caused by the generalized cholinergic actions, remains (17). One way of overcoming this problem is to use an implanted pump system and infuse a cholinomimetic, like bethanechol, directly into the CSF. After studies in animals,

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Harbaugh and colleagues (18) tried this technique in four patients with biopsy proven Alzheimer's disease. Though this was a feasibility study, rather than a clinical trial, improvements were noted which were reversed, or not noted, during placebo infusions. Double-blind techniques were used and the infusions were maintained for several months. This interesting study must be seen as most encouraging for all those researching the therapeutic implications of the cholinergic defect theory of the aetiology of Alzheimer's disease.

Further progress would be greatly assisted if a more specific agonist for the cholinergic system, which is defective in DAT, could be found. The observations of Hammer and colleagues (19) that pirenzipine has a selective antimuscarinic effect with a greater affinity for receptors in glandular tissue, than for muscarinic receptors in heart and smooth muscle, gives hope that cholinergic receptors in different tissues may be pharmacologically recognizably different. This possibility has been advanced by the finding that in mice, pirenzipine has the ability to selectively impair avoidance learning as opposed to other CNS functions (20). A selective agonist for the learning, muscarinic, pirenzipine receptors may be an effective way of treating dementia. RS 86 may be one of a new group of more selective muscarinic agents (21).

OTHER FORMS OF DRUG TREATMENT

Other neurotransmitter systems

There is evidence that other neurotransmitter systems may be defective in DAT. However, it would be difficult to present a case that modification of dopa, 5-hydroxy tryptamine, noradrenaline, or their receptors, can effectively help patients with Alzheimer's disease.

Cerebral vasodilators

Cook and James (22, 23) reviewed cerebral vasodilators in 1981 and produced a classification given in Table 2. Only two drugs, hydergine and nafronyl, probably working in other ways, had some beneficial effects and all vasodilators may reduce blood flow to ischaemic areas. To summarize the results of a large number of studies,

Table 2. Cerebral Vasodilators (from Cook & James (22, 23))

Direct acting drugs	Papaverine
	Cyclandelate
	Nafronyl (Naftidrofuryl)
Drugs acting on adrenoreceptors	Isoxsuprine
	Nylidrin
	Co-dergocrine (Hydergine)
Drugs acting on histamine receptors	Betahistine
Miscellaneous	Vincamine
	Niacin derivatives
	Cinnarizine

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reviewed by Yesavage and colleagues (24) and by Goodnick and Gershon (25), it would seem that there is no good evidence that any group of patients with Alzheimer's disease has been materially helped by an agent which has improved the blood supply to a defective area of the brain.

Cerebro-active drugs

There are a number of drugs which are described as being cerebro-active and are believed to reverse a defect, often of cerebral glucose utilization, which might be one of the causes of brain failure. Suggested actions include: metabolic or neuronal activation, increased energy utilization, neurotransmitter modulation or substitution, and membrane modification. It would be easy to dismiss this group of agents since there is little evidence that a metabolic defect is a major aetiological factor in Alzheimer's disease, and almost no evidence that these agents have a measurable pharmacological effect which could produce a clinical improvement. However, there is an enormous amount of literature on cerebro-active drugs and for some, particularly co-dergocrine, the overall evidence suggests that the drug has some positive therapeutic effects (24, 26, 27). Three drugs are briefly discussed and the others are presented in Table 3.

Table 3. Cerebro-active drugs (based on Spagnoli & Tognoni, 1983 (26))

Drug	Drug type	Modes of action*
Group 1		
Co-dergocrine (Hydergine, dehydroergotoxine)	Ergot derivative mixture	Diverse actions—affect neurotransmitters, oxygen utilization, vasodilatation
Group 2		
Nafronyl	Complex acid ester of diethylamino-ethanol	Vasodilator, promotes glucose utilization and oxidative metabolism
Piracetam	Cyclic derivative of GABA	Increases cerebral ATP effect on phospholipases
Group 3		
Cinnarizine	Piperazine type antihistamine	Calcium antagonism
Vincamine and Eburnamonine	Plant alkaloid derivatives	Vasodilator
Oxypentifylline	Xanthine derivative	Vasodilator

*Modes of action—this is given as a guide only. For some drugs there are many suggested, often unproven, modes of action.

Co-dergocrine (Hydergine). Co-dergocrine consists of four ergopeptine derivatives: dihydroergocornine, dihydroergocristine, dihydro-alpha-ergocryptine and dihydro-

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beta-ergocryptine in a ratio of 3 : 3 : 2 : 1. This mixture of ergot derivatives was first promoted as a cerebral vasodilator. It has now been reclassified among the drugs with mixed effects or the cerebro-active agents. It has been extensively investigated and is one of the most widely used of all drugs.

Co-dergocrine appears capable of modifying many different cerebral functions. It is supposed to increase certain enzymes involved in intermediary metabolism in ganglion cells, alter glucose stores in astrocytes, enhance oxygen utilization and increase EEG amplitude. In addition, because of its chemical similarity to a number of neurotransmitters, it may act at receptor sites specific for noradrenaline, dopamine and serotonin, possibly as an antagonist at the first and as an agonist at the latter two. As a result of these and many other actions, demonstrated in animals, co-dergocrine can be shown to have diverse effects on neurotransmission, hormone release and many other cerebral functions.

The clinically relevant question is: does co-dergocrine delay the progress or reverse the decline in intellectual performance seen in patients with Alzheimer's disease? The large number of trials have been carefully studied by a number of different groups (24, 26, 27, 28) and those which meet certain criteria have been selected for further analysis. The conclusions that are reached are that co-dergocrine: (a) appears able to improve a proportion of the tests of cognitive function and behaviour (b) performs better in these tests than placebo or a simple vasodilator using double-blind techniques but (c) fails to produce an overall, clinically meaningful, improvement. Many would conclude that it is the best agent currently available and would therefore use it. In a dose of 3–4·5 mg daily, it appears to be well tolerated and safe.

A study of the literature reveals several reasons for the uncertainty over the efficacy of co-dergocrine. Firstly, only a small and probably very variable amount of drug reaches the brain, it is not well absorbed, there is a marked first-pass loss, it has difficulty crossing the blood–brain barrier (29, 30) and its effects are non-specific. Secondly, its overall effect appears to be predominantly on mood and responsiveness rather than on memory and cognitive functions which are the basic clinical defects in Alzheimer's disease. Thirdly, most assessments are based on observer scoring systems which tends to make them unreliable. Fourthly, studies over a short period, with relatively small numbers of patients, make the possible long-term benefits impossible to assess. These uncertainties make it very unlikely that co-dergocrine, however widespread its use, will make any major impact on the growing problem of Alzheimer's disease in our ageing population.

Nafronyl. This agent is also called naftidrofuryl. It is a direct-acting vasodilator which may increase brain utilization of glucose and accelerates aerobic brain metabolism in rats (25, 27) and oxidative metabolism in man (31). It is given orally, 100 mg three times daily, but may cause nausea, epigastric pain, diarrhoea, headache and dizziness.

This drug has a low bio-availability and uncertain penetration into the central nervous system. It can be shown to produce some metabolic effects and may improve some parameters on the commonly used rating scales. However, evidence of a reliable clinical improvement in patients with Alzheimer's disease is lacking.

Piracetam. Piracetam (2-oxo-1-pyrolidine acetemide) is a cyclic derivative of gamma-aminobutyric acid (GABA). It is claimed to enhance the efficiency of telencephalic integrative activities. This sort of claim is based on various observations

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made in animal models. Clinical trials which have involved large numbers of patients have not shown evidence of convincing therapeutic efficacy (27, 28, 32).

Miscellaneous

In addition to the groups of drugs discussed above, there are a number of other substances which have been considered as possible agents for patients with DAT.

Peptides. ACTH, vasopressin and various fractions and analogues have been administered in the hope of modifying mental function. This concept has arisen from the observations of de Wied (33) on the influence of the anterior pituitary on avoidance learning and escape behaviour in rats. Short-term studies, on memory function and attention, have yielded some positive results (25, 34, 35) which are of considerable interest. However, attempts to demonstrate long-term benefit in patients with Alzheimer's disease have so far not proved very successful (25, 36, 37).

Naloxone. Reisberg and colleagues (38) have suggested that opioid antagonists may have a role to play in the treatment of dementia. This is because endorphins are believed to contribute to physiological amnesia and encephalins may exert an inhibitory role over various neurotransmitter functions. In a placebo controlled double-blind trial of three doses of intravenous naloxone (1 mg, 5 mg and 10 mg) some statistically significant improvements were noted in a small group of patients with DAT (38). Furthermore, the effects lasted for up to 2 weeks. This must be seen as an interesting observation and the results of further studies, using the oral analogue, naltrexone, are awaited.

Others. Other agents which have been considered worth assessing include α_2 agonists (38), anticonvulsants (38) and L-Dopa (25). Somatostatin, like acetylcholine, has been found to be deficient in the brains of those with DAT. An alternative approach may be to try to increase brain levels of somatostatin (39).

CONCLUSION

There is a bewildering array of drugs available to treat Alzheimer's disease and a very large number of patients who require treatment. Most studies on drugs used to treat this disease are performed badly and tend to show no clinically relevant beneficial effect. The literature makes depressing reading. The doctor tends to regard Alzheimer's as untreatable and all therapeutic agents as useless. This nihilistic attitude is unfortunate since the need for treatment is so great. The way forward must involve a great deal of research into basic mechanisms, and the progress made over the last decade, particularly in relation to the cholinergic deficiency, must be regarded as encouraging. This has to be seen, however, against the uncertainty over whether the cholinergic deficiency is the primary cause, or is secondary to neuronal decay. In addition, there is a greater need for better clinical trials. New treatments must be assessed objectively using double-blind techniques on large groups of reasonably well defined patients who have been treated for a sufficiently long period.

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Short Report

The Action Of Cholinergic Drugs in Experimental Amnesia

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The restoration of the conditioned reactions amnesiated by electro-shock by itself or after the application of "reminder" indicates that the electrocramps interrupt either the process of reinstitution of the traces of memory (2.8.), or lead to it's incomplete disintegration (4.7.). Acting as the agent, reestablishing the amnesiated reactions one applied mainly electrocutaneous stimulation more intensive than during the training and applied to the animal in a situation different from the training situation.

The purpose of the present research is to clarify the possibilities of restoring a conditional avoidance reaction (URI) (CAR) amnesiated by a blockage of the central cholinergic structures by skopolamine or by weakly developed reaction of the subsequent activization of the cholinergic structures by anti-cholinesterazed drug galantamine.

The experiments were performed on 175 mice-males, of the line-

BALB/c. In the first experiment the CAR was achieved in the one combination (5) by applying to the animal electrocutaneous stimulation (3 ma. 1 second) after the animal's transfer from the isolated site into the dark cell with an electrofied floor. The reaction was considered achieved, if the mouse placed on the site 24 hours after the training remained on it for 30 seconds. The preservation of the reaction was checked 24 and 48 hours after the lesson was learned. With 15 of the animals, after the training of CAR, the reaction was achieved in the above described conditions. Second group of animals had a 2.5 mg/kg dose of scapolamine was injected intra-peritoneal 20 minutes before the training. Galantamine (1 mg/kg intraperitoneally) was injected 20 minutes before testing 15 of the mice, whose CAR had been amnesiated both 24 and 48 hours after training, and also to 13 animals on whom the achievement of the reaction have not been done, but who were tested at the exact same times. The 15 amnesiated mice received the "reminders" by the electro-current (10 ma. 1 second) under the condition different from that in which the training have been done. The testing was done 24 hours after the "reminder" and after that, once a week.

For the second experiment, for obtaining a "weak" CAR one used the method by M. Jarvik and B. Kopp (6). One registered the time between the animal's passing from the light part of the cell into the dark part. Immediately after entering, the animal was given a weak (0.1 ma) electrocutaneous stimulation on the paws, which lasted until the mouse did not return back to the lighted part of the cell.

The testing was done after 24 and 48 hours. For this the mouse was placed again into the lighted portion and the latent period of crossing into the dark portion was registered during 5 minutes time. Forty-eight hours after the training and 20 minutes or 24 hours before the testing galantamine was administered (1 mg/kg) intraperitoneally. A part of the animals (13 mice) received the "reminder" by electro-current (10 ma, 1 second). The testing was done 24 hours after the "reminder". The data were processed statistically, by the "chi-square" method and by the Student's criteria (3).

In the control group of mice a CAR was achieved in one hundred (100%) of the animal, after receiving an electracutaneous stimulation (3 ma, 1 second). The achieved reaction was stable and was maintained during the reliable period of observation (nine weeks). With skopolamine administered beforehand, a CAR was achieved by only 40% of the animals, and 60% were amnesiated. The amnesia caused by skopolamine was stable. Only 40% of the animals were observed to have achieved the reaction, after repeated testing. Thereafter, the experiment was done only on those animals, which had not shown a CAR within 24, or 48 hours after training.

Twenty minutes after the galantamine was administered, a CAR was achieved ($P<0.01$) with 53% of the animals, which had received the drug. Twenty-four hours after the galantamine was administered (72 hours after receiving an electrocutaneous stimulation the percentage of animals with CAR increased even more (see table 1). A restored reaction appeared for 5 weeks.

In the control group the preservation of reaction remained at a 100% during the entire 9 weeks of observation.

Application of galantamine in the same dosage to untrained animals did not influence there crossing into the dark cell.

The effect of "reminder" by electro-current was more stable and long lasting. Even nine weeks after the "reminder", a CAR was displayed by 40% of the mice.

In the next experiment we attempted to reinforce the display of (a) weakly developed reaction with the same agents.

With the application of a weak electrocutaneous stimulation (0.1 ma.) the latent period of the mice's crossing over into the dark portion of the cell changed insignificantly upon testing after 24, 48 or 72 hours. Galantamine, administered 48 hours after the application of an electrocutaneous stimulation and 20 minutes before testing, caused a definite ($P<0.05$) increased of this showing twenty-four hours after injection, a further increase of the latent period of crossing over into the dark portion of the cell was observed (table 2). Galantamine had no effect on the achievement of the reaction if the first test was not done against a background of galantamine's action, but 24 hours after it was administered. The "reminder" by the electric-current had a weaker effect.

The results of the experiments demonstrated the possibility of restoring the traces of memory, amnesiated by skopolamine, after the injection of galantamine. In restoring the amnesiated reaction, galantamine in the dosage used is some-what inferior to the "reminder" by electric-current, mainly in the duration

of the effect.

The mechanism of the restoration of the CAR by galantamine may be connected to the effect, nonspecific for memory, of the facilitation of conduction of nervous impulses in cholinergic synapses. Besides, it was demonstrated that the administering of this anticholnesterase substance to the animals leads to the appearance of the emotional reaction of "fear" (1). The latter effect of galantamine, evidently, will be specific for the restoration of memory, insofar as emotional condition appearing under the influence of the drug will be similar to that which accompanies the achievement of the conditioned reaction.

Table 1

The effect of galantamine and of electric "reminder" on the recurrence of CAR, amnesiated by skopolamine.

Groups of Animals	number of animals	Recurrence of CAR % 20 minutes after galantamine	72 hours after training	one week after training
Electrocutaneous stimulation (3 ma, 1 second).	15		100	100
Electrocutaneous stimulation (3 ma 1 second, on the basis of 2.5 mg/kg of skopolamine	24		4	4
Electrocutaneous stimulation (3 ma, 1 second) on the basis 2.5 mg/kg of skopolamine + 1 mg/kg of galantamine	15	53 $P<0.01$	60* $P<0.001$	33 $P<0.05$
Galantamine 1 mg/kg	13	0*	0	0
Electrocutaneous stimulation (3 ma, 1 second) on the basis of 2.5 mg/kg of skopolamine + electric "reminder" (10 ma, 1 second)	15		60 $P<0.001$	73 $P<0.001$

* Twenty-four hours after the administration of galantamine

Table 1

Таблица 1

Действие галантамина и электрического [illegible] на воспроизведение УРП, [illegible] скополамином

Группы животных	Число животных	Воспроизведение УРП, %		
		через [illegible] час после [illegible]	через 72 час после обучения	через одну неделю после обучения
Электрокожное раздражение (3 ма, 1 сек)	15		100	100
Электрокожное раздражение (3 ма, 1 сек) на фоне 2,5 мг/кг скополамина	24		4	4
Электрокожное раздражение (3 ма, 1 сек) на фоне 2,5 мг/кг скополамина + 1 мг/кг галантамина	15	53 $P < 0,01$	60* $P < 0,001$	33 $P < 0,0$[illegible]
Галантамин 1 мг/кг	13	0	0*	0
Электрокожное раздражение (3 ма, 1 сек) на фоне 2,5 мг/кг скополамина + электрическое [illegible] (10 ма, 1 сек)	15		60 $P < 0,001$	73 $P < 0,001$

* Через [illegible] час после введения галантамина.

Table 2

The effect of galantamine and electrical "Reminder" on Recurrence of Weakly Worked Out CAR.

Groups of Animals	number of animals	Latent time of crossing into dark cell after the training. after 24 hours	after 48 hours		after 72 hours.
Electrocutaneous stimulation (0.1ma.)	11	26 ± 14	14 ± 10	21 ± 19	25 ± 19
Electrocutaneous stimulation (0.1 ma) + 1 mg/kg of galantamine 20 minutes before (the) testing.	11	19 ± 13	16 ± 12	101 ± 66*	123 ± 85 P<0.05
Electrocutaneous stimulation (0.1 ma) + 1 mg/kg galantamine 24 hours before testing	12	33 ± 21	P<0.05 18 ± 15		37 ± 31** P>0.05
Galantamine 1 mg/kg 20 minutes before testing	12	15 ± 8	9 ± 6	11 ± 9*	13 ± 9
Electrocutaneous stimulation (0.1 ma) + electric "reminder" (10 ma. 1 second)	11	29 ± 23	17 ± 9		74 ± 64*** P>0.05

* Twenty minutes after administration of galantamine

** Twenty-four hours after administration of galantamine

*** Twenty-four hours after the electric "reminder"..

Table 2

Таблица 2

Эффект галантамина и электрического напоминания на воспроизведение слабовыработанной УРН

Группы животных	Число животных	Латентный период перехода в темную камеру после обучения			
		через 24 час	через 48 час		через 72 час
Электрокожное раздражение (0,1 ма)	11	26±14	14±10	21±19	25±19
Электрокожное раздражение (0,1 ма)+ +1 мг/кг галантамина за 20 мин до тестирования	11	19±13	10±12	101±66* $P<0,05$	123±85 $P<0,05$
Электрокожное раздражение (0,1 ма)+ +1 мг/кг галантамина за 24 час до тестирования	12	33±21	18±15		37±31** $P>0,05$
Галантамин 1 мг/кг за 20 мин до тестирования	12	15±8	0±0	11±6*	13±9
Электрокожное раздражение (0,1 ма)+ + электрическое напоминание (10 ма, 1 сек)	11	20±23	17±9		74±61*** $P>0,05$

* Через 20 мин после введения галантамина.
** Через 24 час после введения галантамина.
*** Через 24 час после электрического напоминания.

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Interrelation Between the Ventral and Dorsal Hippocampus at Improvement and Deterioration of the Short Term Memory

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Most of the numerous physiological and neuropharmacological research during recent years was dedicated to the study of the memory's mechanism, i.e. to the process found in the base of fixation, and the keeping and reproduction of the engram. However, facilitation of the excitement of the synapses and biochemical changes in the brain substrate on which the idea or notion about a short and long lasting memory are based, may lead towards the changes of the functional condition of brain structure. The research of neurophysiologic bases of memory, particularly its regulatory mechanisms does foresee, first of all, the study of the functional conditions of separated brain structures, and their relationship in the memory process (2,3). According to existing conception, the limbic system in general, but particularly the hippocampus, plays an important part in the memory process (1,5,9,10,18,31). Our research indicates (3,13) that an improvement in the short term memory, which has been induced

by the action of pharmacological substances is followed by a decrease in the level of excitement in the dorsal hippocampus, especially in the areas within fields CA_3 and CA_2. On the contrary, the deterioration of the short term memory is characterized by an augmented excitement of the dorsal hippocampus. The research of many authors (20,21,30) indicates the presence of functional differentiation in the realms of the dorsal and ventral hippocampus. The aim of our work is to study the functional condition of the ventral hippocampus and its relation to the dorsal hippocampus, with a focus on the improvement and deterioration of the short term memory as conditioned by the action of different neurotropic substances.

Methodics

The research was done on six dogs and ten rabbits, with the bipolar electrodes permanently implanted into different formations of the head brain, under the condition of the free behaviors of the animals (12).

In the first part of the work, executed only on 6 dogs, the influence of the neurotropic substances on the memory was studied. The experiments were done in a large experimental room, using the methodics of the delayed reactions, which is a well known test for the short term memory (1,11). According to methods of P. S. Kupalov (14), after the dogs had learned strong conditioned reflexes to food in the form of running to three automatic feeders (14), one began the study of the delayed reactions.

During these experiments the animals were on the start square in a closed cage. One turned on light or sound signaling the feeding in one of three feeders. The cage automatically opened after an increasing period of time. If the animal had correctly chosen the feeder, it received the meat. If the choice was wrong the food was not served, i.e. to get the food the dog should remember the signal given earlier. In this way one determined the maximal time of delayed reactions connected with the conditional stimulants and the duration of the short-term memory caused by remembering the whereabouts of the food in different situations under the experimental conditions. Four screens were placed at the distance of two to three meters in front of, and at the side of the cage in which the dog was located. The dog was released from the cage after an increasing period of time. If the animal walked directly to the location of the meat without searching movements, the reaction was considered correct.

In the second part of the research also performed on six dogs, one studied the influence of neurotropic substances on the functional condition of the ventral hippocampus and its relationship with the dorsal hippocampus. The effects of the pharmacologic substances on different parts of the hippocampus were also studied on the rabbits. The effects of the functional condition of the ventral and dorsal hippocampus were expressed by the level of their excitability, which was determined by the correlation caused by minimal threshold electro stimulation of

this brain formation and accompanying EEG reactions.) For stimulation of the hippocampus, (frequency 50g/z, duration of impulse 1 m sec, duration of stimulation 5 sec.)one used a 2-channel generator of right angle impulses with the high frequency additions. When studying the character of correlations between the ventral and dorsal hippocampus, one investigated the effect of preliminary subthreshold and threshold stimulation of one part of this structure at the level of excitability of the other. Notations of bio-potentials were done on the 16 channel electroencyphelograph "Biofizprelor" (bio-physical device). The research substances galantamine (-0,3-0,5 mg/kg, ethymisol -1-3, phenamine -0,1-0,2, strychnine -0,03, caffeine -3-15, methamysil -0,1, atropine -0 5-1, amenasine -3, reserpine -0,05 mg/kg) were given to the dogs intramuscularly and per. os. Doses of the substances were equal when researching the dogs memory and when studying the influence of preparations on the functional condition of the hippocampus. When studying the effects of the substances on the excitability of the hippocampus of rabbits, the doses usually were larger than the above mentioned. In this experiment galantamine was applied in the doses of 1 mg/kg, ethymisal -4, phenamine -2, strychnine 09,1, caffeine -20, methamysil -1, atropine -2, aminasine -5, reserpine -1 mg/kg. After finishing the experiments the morphologic control of the localization of electrodes was performed. (See table on page 34.)

Table, page 34

The influence of the neurotropic substances on the short term memory, and the level of excitability of ventral and dorsal hippocampus of dogs.

Substance	Dose mg/kg	Short term memory	Hippocampus ventral	Hippocampus dorsal
Galantamine	0,4	Improvement	+	+
Phenamine	0,2	"	+	-
Strycnnine	0,03	"	+	-
Ethymisole	2,0	"	+	-
Caffeine	15,0	No change	-	-
Methamisyl	0,1	Deterioration	+	+
Atropine	1,0	"	+	+
Aminasine	3,0	"	+	+
Reserpine	0,05	"	+	+

Note: "+" - encreasing of excitability;
"-" - decreasing of excitability.

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[illegible]	[illegible]	[illegible]	[illegible]	
			[illegible]	[illegible]
Галантамин	0,4	Улучшает	+	—
Фенамин	0,2	»	+	—
Стрихнин	0,03	»	+	—
Этимизол	2,0	»	+	—
Кофеин	15,0	Не изменяет	—	—
Метамизил	0,1	Улучшает	+	+
Атропин	1,0	»	+	+
Амизил	3,0	»	+	+
Резерпин	0,05	»	+	+

Примечание. «+» — повышение возбудимости; «—» — снижение возбудимости.

The Result of Research

Under the condition of our experiments, the maximum time of the postponed reactions of the dogs, determined by their remembering the location of the food under different situations of the experimental condition, and the conditional stimulant has been 13 and 4 minutes on average. On the basis of the influence of phenamine, ethymisol, strychnine and anti-cholinesterase the substances of galantamine (see the table) the animals short term memory was credibly improved. The maximum time of the delayed reaction defined by the conditional signals and screens was most clearly augmented by the introduction of phenamine and ethymisol (on the average 100%), and in a lesser degree when applying strychnine and galantamine (on the average 60%). The range of doses of caffein in the research did not change the short-term memory of animals. The blocking of the M-holinoreactive systems of the brain by means of methamysil and atropine, diminishing of the reserves of cateholamines with the help of reserpine, and also the introduction of aminasine, which possesses a wide spectrum of pharmacologic action led to the worsening of the short-term memory in all experiments. The most notable maximum time of delayed reaction with the dogs diminished on the background of activity of methamysil and atropine (on the average 83%), and to a lesser degree when applying aminasine (on the average 25%). The maximum effect of reserpine usually appeared 8-12 hours after the one time injection. In this case the time of the delayed reactions

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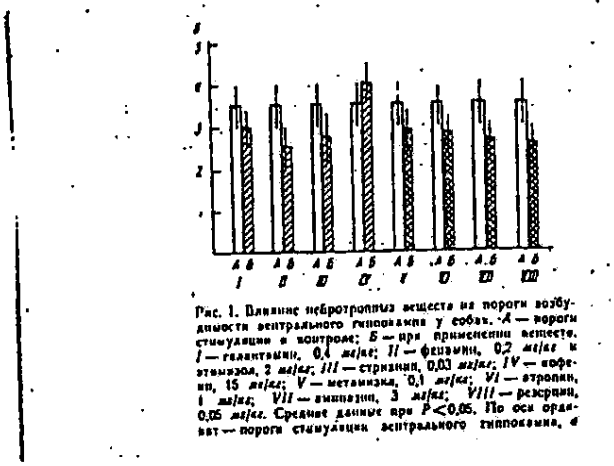

Рис. 1. Влияние нейротропных веществ на пороги возбудимости вентрального гиппокампа у собак. *А* — пороги стимуляции в контроле; *Б* — при применении вещества. *I* — галантамин, 0,4 *мг/кг*; *II* — фенамин, 0,2 *мг/кг* и этимизол, 2 *мг/кг*; *III* — стрихнин, 0,03 *мг/кг*; *IV* — кофеин, 15 *мг/кг*; *V* — метамизол, 0,1 *мг/кг*; *VI* — атропин, 1 *мг/кг*; *VII* — аминазин, 3 *мг/кг*; *VIII* — резерпин, 0,05 *мг/кг*. Средние данные при $P<0,05$. По оси ординат — пороги стимуляции вентрального гиппокампа, в

Fig. 1 Influence of the neurotropic substances on the thresholds of the excitability of the ventral hippocampus by the dogs. A - the thresholds of stimulation in control. B - by applying the substances. I-galantamine, 0,4 mg/kg; II-phenamine 0,2 mg/kg and ethymisal 2 mg/kg, III strychnine, 0,03 mg/kg, IV caffeine 15 mg/kg, V methamysil, 0,1 mg/kg, VI atropine 1 mg/kg, VII aminasine, 3 mg/kg, VIII reserpine, 0,05 mg/kg. Average data at (P) R<0.05. On the axis of ordinates - the thresholds of stimulation of the ventral hippocampus, b. (Page 35)

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Interrelation Between the Ventral and Dorsal Hippocampus at Improvement and Determination of the Short Term Memory

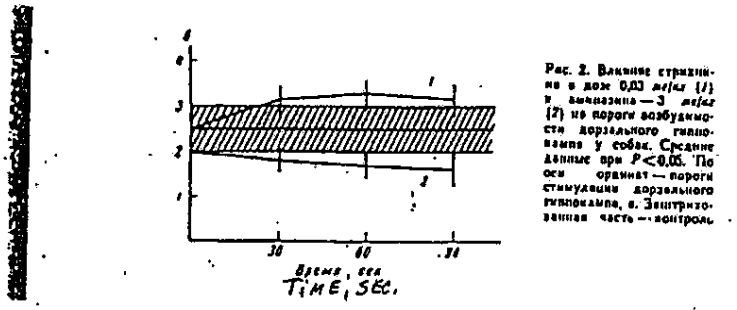

Рис. 2. Влияние стрихнина в доз 0,03 мг/кг (1) и аминазина — 3 мг/кг (2) на пороги возбудимости дорзального гиппокампа у собак. Средние данные при $P<0,05$. По оси ординат — пороги стимуляции дорзального гиппокампа, в. Заштрихованная часть — контроль.

Fig. 2 The influence of strychnine, dose -0,03 mg/kg (1) and aminasine -3. mg/kg. (2) on the excitability thresholds of the dog's dorsal hippocampus. Average data at $P<0,05$. on the ordinate axis - (are) the thresholds of the dorsal of the hippocampus stimulation. (6) Shaded part - control.

(Page 36)

diminished 25%. The introduction of reserpine to the animals during 3 or 4 days led to a more expressed worsening of the short-term memory. (See table on p. 35)

The research on the functional condition of the ventral hippocampus when applying the substances which improve the short-term memory has proven that galantamine, ethymisol, phenamine and strychnine are assisting the raising of the level of excitability of this structure of the brain with the dogs as well as with rabbits. On the basis of the action of the ethymisol and phenamine, the excitability of the ventral hippocampus raised on the average 25%, when applying strychnine it was raised 18%. The effect of galantamine was less expressed. In these experiments the thresholds of the stimulation of the ventral hippocampus lowered on the average 12%. On the contrary, on the basis of the activity of different doses of caffeine, which did not change the maximum time of the delayed reaction of the dogs, the thresholds of stimulation of the ventral hippocampus rose 10 to 15%; that means to say, one observed the lowering of the excitability of this formation. Side by side with the group of substances improving the short-term memory and at the same time augmenting the level of excitability of the ventral hippocampus, the substances worsening it, also acted to lower the thresholds of stimulation of this structure of the brain. In these experiments, methamysil, atropine, aminosine and reserpine raised the excitability of the ventral hippocampus 10-20% with the dogs as well as the

rabbits and the most expressed stimulating influence was done by reserpine (See table on page 35).

When studying the functional condition of the dorsal hippocampus on the basis of the activity of the substances improving the short-term memory, it became clear that phenomine, ethymisol, strychnine and galantamine, contrary to their effects on the ventral hippocampus, lower the level of excitability of its dorsal part with the dogs and the rabbits. In this case, the thresholds of stimulation of the dorsal hippocampus was raised 10-18% compared to the former conditions. Anological influence on this structure was performed by caffeine. The substances contributing to the lowering of the maximum time of delayed reactions of the dogs, on the contrary, raised the excitability of the dorsal part of the hippocampus. The thresholds of its stimulations on the basis of the activity of methamysil, atropine, aminasine and also after the preliminary introduction of reserpine were lowered 15-25% (picture 2, page 36).

At the same time, with neuropharmacologic analysis of the functional condition of the ventral and dorsal hippocampus in regard to improvement and the deterioration of the memory of the dogs, there were experiments done which studied the influence of the subthreshold and the threshold electro-stimulation of those formations on the short-term memory (figure 3 & 4, page 36). A minimal tension current was applied at the

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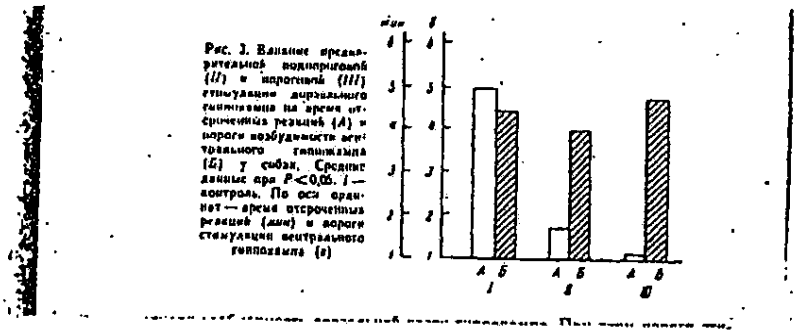

Рис. 3. Влияние предварительной подпороговой (II) и пороговой (III) стимуляции дорзального гиппокампа на время отсроченных реакций (А) и порога возбудимости вентрального гиппокампа (Б) у собак. Средние данные при $P<0,05$. I — контроль. По оси ординат — время отсроченных реакций (*мин*) и порога стимуляции вентрального гиппокампа (*в*)

Fig. 3 Influence of the preliminary subthreshold (11) and threshold (111) stimulation of the dorsal hippocampus on the time of the delayed reaction (A) and the thresholds of excitability of the dog's ventral hippocampus, (B) Average data at $P<0.05$ 1- control. On the ordinate axes - the time of the delayed reactions (minutes) and the thresholds of stimulation of the ventral hippocamus, b. (Page 36)

threshold of stimulation which promoted the appearance on E.G. the hippocampus, and consequential formations of brain discharges, which did not provoke the epilepti-forming reactions. The indicators of the subthreshold stimulation were usually 10-15% lower than the threshold ones. In this case the consequential discharges were not observed. It became clear that the threshold stimulation of the ventral and of the dorsal hippocampus, in the beginning of the delayed reaction, led to a sharp worsening of the short-term memory. Subsequently, the consequential discharges most often irradiated from the hippocampus into mesencephalitic reticular formation, frontal and posterior hippocampus, and less so into the occipotal and temporal part of the cortex. On the contrary, the subthreshold stimulation of the ventral hippocampus contributed to the improvement of the short-term memory of the animals. In these experiments, the maximal time of the delayed reaction increased 27% on the average.

After the clarification of the effects of the subthreshold and threshold stimulation of the dorsal and ventrical hippocampus for the short-term memory, given the same intervals, the correlations between the given structures on the same animals were investigated (See picture 3 and 4, page 37). It was found that the preliminary threshold stimulation of the ventral hippocampus led to the lowering of the level of excitability of its dorsal part on the average 14%. However, if

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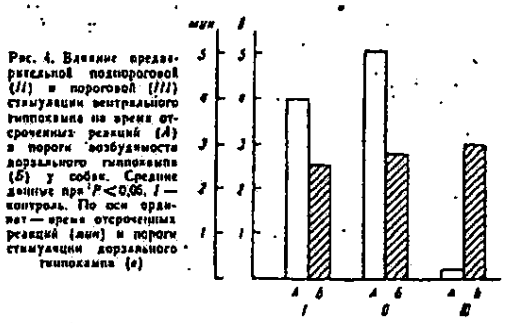

Рис. 4. Влияние предварительной подпороговой (II) и пороговой (III) стимуляции вентрального гиппокампа на время отсроченных реакций (А) и пороги возбудимости дорзального гиппокампа (Б) у собак. Средние данные при $P<0,05$. I — контроль. По оси ординат — время отсроченных реакций (мин) и пороги стимуляции дорзального гиппокампа (в)

Fig. 4 The influence of the preliminary subthreshold (11) and the threshold (111) stimulation of the ventral hippocampus on the time of the delayed reactions (A) and the thresholds of excitability of the dog's dorsal hippocampus (B). Average data at $P<0,05$, 1 - control. On the axis of ordinates - the time of delayed reactions (minutes) and the thresholds of the stimulation of the dorsal hippocampus (6). (Page 37)

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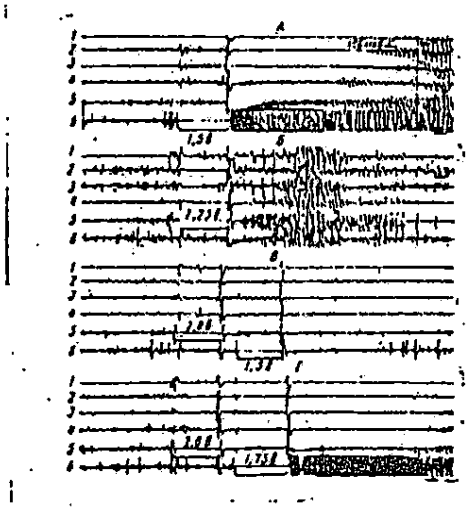

Fig. 5 The influence of subthreshold stimulation of the ventral hippocampus of a dog on the excitability level of the dorsal part of this brain structure. A - EEG by threshold stimulation of the dorsal hippocampus; B - EEG by threshold stimulation of the ventral hippocampus; C, D - influence of the preliminary subthreshold stimulation of the ventral hippocampus on the excitability of the dorsal hippocampus. 1 - frontal cortex; 2 - temporal cortex, 3 - occipital cortex; 4 - caudate nucleus 5 - ventral hippocampus; 6 - dorsal hippocampus. Horizontal line is the period of stimulation. (Pg 37)

from the biginning the threshold stimulation of the dorsal part of the structure was performed, the excitability of the ventral hippocampus lowered less expressively, and in some experiments it did not change at all. In these experiments, the termination of the functional condition of any part of the hippocampus was performed immediately after the ending of the consequential discharges on E.G. caused by threshold stimulation of the other part of this formation. In the experiments in which correlations between the ventral and dorsal hippocampus were checked at their subthreshold stimulation, the following stimulation of the second structure was performed two seconds after the determination of the stimulation of the first one. It has been established that the subthreshold stimulation of the dorsal hippocampus, leading to the deterioration of the short-term memory of the dogs, contributed to the increase of the level of excitability of the ventral part on the average 15%. On the contrary, the subthreshold stimulation of the ventral hippocamus, causing the improvement of the short-term memory, led to the lowering of excitability of the dorsal part of the structure 10% (See picture 4 and 5, page 38).

The Review of the Results

At present there are numerous papers pointing to the active part played by the hippocampus in the process of the memory (1,4,5,7,10,15,17,18,22,26,27,31). Most of the authors believe that the hippocampus is taking part in the process of the

engram formation. The dorsal and ventral parts of this structure are considered as similar, but not identical formations (20). The influence of the stimulation of the dorsal and ventral hipoocampus on the duration of the delayed reaction was also demonstrated (7). However, the functional condition of the ventral and dorsal hippocampus, and also their correlations when elevating or lowering the level of the short-term memory, caused, in particular, by the introduction of pharmacological substances, was not yet studied.

Past investigations have demonstrated that the elevation of the level of endogenous acetycholine caused by an anticholinesterase substance, galantamine; the release of a cateholamine from the extragranular functionally active depository, caused by phenamine, and the application of stimulators of strychnine and ethymisol leads to the improvement of the short-term memory, which develops in connection with the increase of the level of excitability of the ventral hippocampus and the lowering of the excitability of the dorsal part of this structure. On the contrary, the blocking of the central M-holinoreceptors, caused by methamysil and atropine, the depletion of the storage of cateholamine, neuroadrenaline, adrenaline and serotonine, which was achieved by the effects of reserpine and also the introduction of aminasine, possessing adrenolitic effects on the halinolitec and antihistamic activity, furthered the maximal time of delayed reaction in the dogs, and on an accompanied lowering of the maximal time of delayed reactions

by the dogs, which was accompanied at the same time by the rise of excitability of the ventral and the dorsal hippocampus. In this case, where the short-term memory was not changed as it was demonstrated with the use of caffeine, one observed the lowering of the level of excitability of the dorsal and ventral part of this structure.

Consequently, neurotropic substances, which work differently on the central action are able to strongly regulate the functional condition of the hippocampus in the process of the improvement and deterioration of the memory.

At the present time most of the research is about the influence of different neurotropic substances on the proper mechanisms of memory, that means to say, on the process of fixation, consolidation and recreation of the engrams (10, 19,24). Most of the research comes to the conclusion that in breaching the problem of the memory the determinants are the displacement in the synthesis of the ferments of the system of acetycholines-acetiholinesterase and the proteins of the synaptic membranes (10). In this respect, the important data was received from S.N. Golikov with co-authors (6), which indicated that the rise of the conditional reflexes is observed only in the case when acetilholinesterase is blocked 13-16%; the blocking of the ferments for 25% and more leads to contrary effects. We accept the standpoint of R. Yu. Iliyouchenko (10), Deutsch (24) and others; according to this viewpoint, the cholinergic mechanisms are the link, the systems which are basic to the formation of the engrams.

However, for the normal functioning of the hippocampus and other brain formations in the memory processes, it is important, probably the optimal interaction of biogene amines in side of them. This interaction may depend on the functional meaning of a given brain structure, and it can be directed by influencing first of all the holinoreactive systems. According to Kele (28), acetylcholine, besides acting as a basic mediator, can facilitate the release of noradrenaline. At the same time, noradrenaline improves the processes of the bio-synthese of aceticholine (32), and also increases its level in the brain structures (29). In our experiments, phenamine demonstrated similar affect on memory and the functional condition of the hippocampus, as galantamine, strychnine, and ethymisol. In addition, phenamine augmented the release of catecholamines and increased the release of acetylcholine, which in turn influenced the ends of the neurons which contained catecholamines and synapsed at the cholinergic neurons in the rostral part of the brain (25). According to St. Dobreva and his co-authors, caffeine is more influential than phenamine in blocking the activity of acetilcholinesterase in the brain. However, caffeine, unlike phenamine, does not cause an increase in the secretion of noradrenaline in the brain's perfuzate (23). Apparently, the absence of the stimulating affect of caffeine on the delayed reactions of the dogs and its distinctive effect on the level of excitability of the dorsal and ventral hippocampus,

observed in our experiments, may be connected with this data.

R.I. Kruglikov thinks (15) that the consolidation process, which is closely connected with the hippocampus, of a metabolic nature. It is possible that various neurotropic substances which improve and deteriorate the memory may produce a monodirectional effect, at least at the last stages on these metabolic processes, either increasing or decreasing them. This supposition is corroborated in our experiments in which we were able to achieve a change of the level of the dog's short-term memory by means of electrical stimulation of the dorsal and ventrical hippocampus. In this case, the stimulation of the ventral hippocampus using current parameters lower than the threshold of 10-15% to provoke discharges of after effects on E.G. caused the improvement of the short-term memory, and at the same time, the simultaneous lowering of the excitability of the dorsal hippocampus. On the contrary, the analogic stimulation of the dorsal hippocampus made for the deterioration of the short-term memory of the animals, and at the same time made for an increase in the excitability level of the ventral part of this structure. This means that the character of the co-relations between the ventral and dorsal hippocampus in these experiments coincided with the above mentioned experimental results, in which was performed the pharmacological analysis of the excitability of the ventral and dorsal parts of the hippocampus to improve and deteriorate the short-term memory.

In this way, our research has shown that the improvement and deterioration of the short-term memory coincides with various functional conditions of the hippocampus. The interrelations between ventral and dorsal parts of this structure, define, to a significant degree, the basic mechanisms which are involved in the improvement and deterioration of the short-term memory. As the hippocampus is only a small part over the very active and complicated brain, it cannot explain these mechanisms.

Deductions

1. An improvement in the short-term memory, which is caused by neurotropic substances which have a central effect (phenamine, ethymisol, strychnine, galantamine), is followed by an elevation of the level of excitability of the ventral hippocampus and lowering of the excitability of the dorsal part of this structure.

2. The deterioration of the short-term memory, caused by methamysil, atropine, aminasine and reserpine, occurs on the basis of heightened excitability of both the ventral and dorsal hippocampus.

3. Given an improvement of the short-term memory which is caused by electro-stimulation of the ventral hippocampus, there is observed a lowering of the excitability level of the dorsal hippocampus.

4. With the deterioration of the short-term memory, caused by electrostimulation of the dorsal hippocampus, there is observed an elevation of the excitability level of the ventral part of this structure.

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bonnie DAVIS
Serial No.: 819,141 Group No.: 125
Filed: January 15, 1986 Examiner: Friedman
For: METHOD OF TREATING ALZHEIMER'S DISEASE

Commissioner of Patents and Trademarks
Washington, D.C. 20231

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SIR:

L E T T E R

The purpose of this letter is to submit the documents referred to of the response of September 9 that were not submitted therewith, to clarify the remarks in that response to certain of these references and to submit copies of additional pieces of art which have come to light since that response was filed.

We now enclose copies of the following:

Acta Anesth Scand (1980) 21:166 referred to on page 2 of the response;

English translation of Summary of Russian language paper in Biull Exp Biol Med (1977) 83:185 referred to on page 5 of the response;

Psychopharmacology (1977) 52:251, referred to on page 5 of the response;

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231

JOHN RICHARDS
(Type or print name of person mailing paper)

Date: December 15, 1986

(Signature of person mailing paper)

J Am Geriat Soc 1977 25:1, referred to on page 5 and 8 of the response;

Pages 582-3 of The Pharmacological Basis of Therapeutics referred to on page 6 of the response;

Strategies for the Effective Treatment for Senile Dementia, p 177 referred to on pages 6 and 8 of the response;

Behavioral Biology (976) 16 p 387 referred to on page 6 of the response;

J Pharm Pharmac (1977) 29:110, referred to on pages 6 and 7 of the response;

Pharmacol Biochem Behav (1976) 5:(Suppl.1) 41, referred to on page 6 of the response;

Physiol Behav (1975) 14:563, referred to on page 6 of the response;

Pharmacol Biochem Behav (1974) 2:663, referred to on page 6 of the response;

Physiol Behav (1974) 13:381, referred to on page 7 of the response;

Hormones, Behavior and Psychopathology, pages 1, 3, 4 and 6-8 referred to on pages 7 and twice on page 8 of the response;

Neural Mechanisms in Learning and Memory, p 483 referred to twice on page 7 and twice on page 8 of the response;

Pharmacol Biochem Behav (1976) 4:703, referred to three times on page 7 of the response;

Pharmacol Biochem Behav (1974) 2:557, referred to twice on page 7 of the response;

Behav Biol (1977) 20:168, referred to on page 7 and twice on page 8 of the response;

English Summary of Arzneim-Forsch (1976) 26:1947, referred to on page 7 of the response;

Acta Physiol Pharmacol Bulg (1976)2:49, referred to twice on page 7 of the response;

Behav Biol (1975) 15:245), referred to on page 7 of the response;

Brain Res (1975) 84:329, referred to on page 7 of the response;

Arch Int Pharmacodyn (1974) 211:123), referred to on page 7 of the response;

Neural Mechanisms in Learning and Memory, p.508, referred to on pages 7 and 8 of the response;

Pharmacol Biochem Behav (1976) 4:123, referred to on page 7 of the response;

Curr Med Res Opin (1976) 4:303, referred to on page 8 of the response;

Psychopharmacology (1976) 49:307, referred to on page 8 of the response;

J Nerv Ment Dis (1976) 163:59, referred to on page 8 of the response;

J Comp Physiol Psychol (1976) 90:1082, referred to on page 8 of the response;

Psychopharmacology: A Generation of Progress, p. 1525 referred to on page 9 of the response;

J Am Geriat Soc (1977) 25:289, referred to on page 9 of the response; and

Neurobiology of Aging (1985) 6:95, referred to on page 9 of the response.

Copies of J Med Chem (1986) 29:1125 referred to on pages 6 and 8 and of J Clin Hosp Pharmac (1985) 10:327 referred to on pages 2, 8 and 9 of the response were submitted with the previous response.

A review of these references has revealed a few minor

discrepancies in the previous response as filed, although these do not affect the validity of any of the submissions made.

First at page 5, line 28 of the response, the specific reference to methamphetamine is misleading since the reference does not refer to this drug. The substance of statement made is, however, correct. The reference in fact refers to the use of methylphenidate. According to Goodman et al , the Pharmacological Basis of Therapeutics, methylphenidate is therapeutically interchangeable with the amphetamines.

At page 5, line 30, the reference to J Am Geriat Soc is wrong. The reference should have been to J Med Chem (1986) 29:1125.

There is a typographical error at page 6, line 22 of the response. As is clear from the papers referred to three year period in question was 1974-77.

A reconsideration of the papers listed as showing prior studies of compounds said to have effect on the facilitation of memory in humans or animals without brain lesions leads to a conclusion that the total number of compounds noted rather than being 39 should have been either 37 or 45 depending upon whether each of the ACTH fragments noted in the Hormones Behavior and Psychopathology reference is regarded as being one or several compounds.

At page 7, line 17, the reference cited in support of the studies on imipramine was wrong. It should have been Rosenzweig MR, Bennett EL eds Neural Mechanisms in Learning and Memory MIT Press Cambridge p. 483. A copy is enclosed.

At page 7, line 18, the reference support in support of studies on ß-lipotropin was wrong. The correct reference was J Pharm Pharmac 29:110. A copy is enclosed.

At page 8, line 6, the second reference to studies on strychnine is wrong. The correct reference is Acta Physiol Pharm Bulg (1976) 2:66. A copy is enclosed.

At page 8, line 19 "ACTH 4-10" should read "ACTH fragments" as the second reference used ACTH 4-9. However, any fragment of ACTH 1-10 containing 4-7 has equal potency. (Hormones, Behavior and Psychopathology, Sachar, 1976, p. 3).

At page 8, line 25, the second reference to studies using methylphenidate is wrong. The correct reference is J Med Chem 29:1125.

Furthermore, the reference to J Am Geriat Soc (1977) 25:289 should be ignored in the discussion of vasopressin at page 9, line 3 since the article does not refer to this compound, although the other two papers cited do so.

Finally, the applicant wishes to draw the Examiner's attention to some additional pieces of prior art that have only now been found or of which she was aware previously, but had not looked at for a prolonged period that contain information relating to the properties of galanthamine. These are as follows:

Baraka & Harik JAMA Vol. 238 pages 2293-4 (1977) - discusses use of galanthamine to reverse scopolamine-induced central anticholinergic syndrome;

Tonkopii and Prozorovskii in Byul Eks Bio i Med Vol. 82 pages 823-25, available in translation from Plenum Publishing Co., New York describe a study of the interaction of galanthamine in mouse brain acetylcholinesterase in vivo;

Wislicki in Brit J Anaesthesia 39:963 (1967) compares galanthamine with neostigmine as an antagonist non-depolarizing muscle relaxants;